University of Alberta

The Role of Transcranial Doppler Ultrasonography in the Diagnosis of Cerebral Vasospasm following Aneursymal Subarachnoid Hemorrhage

by

Yashail Y. Vora

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

in

Experimental Surgery

Department of Surgery

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Abstract

Objectives: Transcranial Doppler (TCD) is routinely employed to diagnose cerebral vasospasm following subarachnoid hemorrhage. The predictive value of TCD velocities for angiographic vasospasm (AV) was determined.

Methods: Aneurysmal subarachnoid hemorrhage patients between Jan/1994-May/1997 were retrospectively reviewed. AV on follow-up angiograms was independently graded by 2 blinded observers. Middle cerebral artery velocities were correlated with clinically significant AV.

Results: 101 patients were included. Interobserver agreement for AV was good (kappa 0.86). The NPV of velocities <120 cm/s was 94% but ranged from 75% to 77% for velocities ≥120 cm/s. The PPV of velocities ≥200 cm/s was 87%, but only 44% to 56% for <200 cm/s. 51% of patients fell in the <120 or ≥200 cm/s range.

Conclusions: Only the very low or high absolute velocities (<120 or ≥200 cm/s) were sufficiently useful to guide clinical management in the individual patient. Absolute velocities were of limited use in half the patients.

Dedication

I dedicate this work to my parents, Shaila and Yeshvant Vora, to whom I owe all my successes and achievements.

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The mastermind behind this study was Dr. Findlay. Without his direction and vision this work would not have been realized. Dr. Steinke's constant guidance and support was invaluable and was much appreciated. I am grateful to Dr. Suarez-Almazor for her advice regarding the application of rigorous epidemiological methodology for scientific investigations and for her assistance with the statistical analysis of the results.

I would also like to thank the staff of Medical Records and the Radiology Film Library for their support of this project. Finally, an experienced and skillful team of TCD technologists was responsible for the measurement of the TCD velocities upon which this study is based; without their contribution this study would not have been possible.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ACA	Anterior cerebral artery
AV	Angiographic vasospasm
CBF	Cerebral blood flow
CVP	Central venous pressure
CPP	Cerebral perfusion pressure
DIND	Delayed ischemic neurologic deficit
EC-ICA	Extracranial internal carotid artery
F/U	Follow-up
FV	Flow velocity
HT	Hyperdynamic therapy
IC-ICA	Intracranial internal carotid artery
ICP	Intracranial pressure
LR	Lindegaard ratio
LR +, LR-	Likelihood ratio for a positive and negative test respectively
MCA	Middle cerebral artery
NPV	Negative predictive velocity
PCA	Posterior cerebral velocity
PPV	Positive predictive value
SAH	Subarachnoid hemorrhage
SC-ICA	Supraclinoid internal carotid artery
Se	Sensitivity
Sp	Specificity
TCD	Transcranial Doppler
U/S	Ultrasound
Vs.	Versus

CHAPTER 1: INTRODUCTION

I. History of Transcranial Doppler

The Doppler principle was first formulated by the Austrian physicist Christian Doppler and presented at the Royal Bohemian Society of Sciences in Prague in 1842. It was later experimentally verified in 1845 by the Dutch physicist Buys Ballot who used a band of trumpeters on an open car being drawn by a locomotive traveling at 65 km/h (1, 2). The Doppler effect is described below in section II. Although the use of ultrasound (U/S) to evaluate intracerebral lesions in situ had been described as early as 1951 (3), its application to the measurement of blood flow using the Doppler principle was first reported in1959 by Satomura who investigated flow patterns in peripheral arteries (4). In 1965 Miyazaki and Kato recorded blood flow velocity (FV) in the extracranial arteries supplying the brain (5). Doppler ultrasonography has been routinely employed for cardiovascular indications for over 25 years; cardiac Dopplers have been commercially available since the early 1970's (1).

The use of Doppler to study the intracranial circulation was reported in 1979 by Nornes who used it to evaluate cerebral hemodynamics in arteriovenous malformations (AVM) and saccular aneurysms intraoperatively with the cerebrum exposed (6, 7). All above applications used relatively high frequency ultrasound (5 - 10 MHz) which penetrates cancellous bone poorly. Hence the skull presented a natural barrier that hindered the development of transcranial Doppler (TCD) through intact bone for over 20 years. This was first accomplished in1982, in Bern,

Switzerland, by Aaslid, Markwalder & Nornes using lower frequency ultrasound (2 MHz) which is better able to penetrate bone (8). Since its inception, Doppler ultrasonography and its applications have undergone a remarkable evolution and steady progress to the point today when one is able to visualize the intracranial vasculature using transcranial color-coded duplex ultrasound (TCCD). This is described in Section VII.

II. Principle of Transcranial Doppler Ultrasound

A) The Doppler Principle

The Doppler effect refers to a shift in the frequency of a wave when either the transmitter of the wave or the receiver is moving relative to each other (9). Although this effect is most commonly experienced with sound, it applies to all waves. According to this principle, sound waves reflected back from an object traveling toward the receiver will have a higher frequency, and those reflected off an object moving away from the receiver will have a lower frequency, compared to that of the incident sound waves. For the purposes of measuring flow velocities (FV) in blood vessels, the red blood cell becomes the moving object and an U/S emitting probe is the transmitter as well as the receiver. The velocity can be calculated from the frequency shift of the reflected waves using Fast Fourier transformation (10, 11).

B) The Physics of Doppler

Ultrasound refers to sound with frequencies above 20,000 Hz which are beyond the human ear's range of hearing. Sonar penetration through intact skull is

better at lower frequencies compared to the 5-10 MHz frequencies typically employed for other applications (8, 12). Therefore most TCD instruments use U/S frequency of 2 MHz. The frequency shift of the reflected U/S is proportional to the speed and direction of the moving red blood cell or blood flow. The mathematical relationship between the shift in frequency and the velocity can be derived as follows in two steps (1, 2):

Step 1: Determine the frequency f_1 received by a red blood cell (RBC) moving with velocity V_{RBC}

Step 2: Determine the reflected frequency f_2 received back by the stationary transducer.

Assume the propagation velocity of U/S is V_{US} and the initial transmitted wave's frequency and wavelength are f_0 and W_o respectively. In general,

$V = f w$ .....**(i),** where V is the velocity of a wave, f is its frequency and w is its wavelength.

Step1: If a RBC is at rest then the number of waves that will travel past it in time t is:

$$\frac{V_{US}\ t}{W_o} \text{.....(ii)}$$

Because the RBC is moving either toward or away from the source of the U/S, the velocity with which it meets the waves will be $V_{US} + V_{RBC}$ if the movement is toward the transmitter, or $V_{US} - V_{RBC}$ if it is away.

The number of waves that will pass the *moving* RBC in time t is:

$$\frac{(V_{US} +/(-)\ V_{RBC})\ t}{W_o} \text{.....(iii)}$$

Hence the frequency f_1 perceived by the RBC is:

$$f_1 = \frac{\#\text{ waves}}{t} \quad \text{or} \quad \frac{(V_{US} +/(-)\ V_{RBC})\,t}{(W_o)\,t} = \frac{V_{US} +/(-)\ V_{RBC}}{W_o} \quad \text{.....(iv)}$$

$$W_o = \frac{V_{US}}{f_o} \quad \text{from equation (i)}$$

Therefore, $\boxed{f_1 = fo\ \frac{(V_{US} +/(-)\ V_{RBC})}{V_{US}}}$ ..... **(v)**

Please note that in the above equations whether the "+" or "-" is used depends on whether the RBC is moving toward the U/S waves or away from it.

Step2: In the second step the RBC becomes the transmitter as it reflects back the incident waves of frequency f_1, and the U/S probe becomes the receiver. Let T be the period of oscillation of the sound wave.

$T_1 = 1 / f_1$. During this interval the RBC moves toward the detector by a distance,

$$V_{RBC}\,T_1 = \frac{V_{RBC}}{f_1}$$

Therefore the wavelength W_2 of sound waves arriving back at the TCD probe is not just V_{US} / f_1 but it is,

$\frac{V_{US} - V_{RBC}}{f_1}$ or, $\frac{V_{US} + V_{RBC}}{f_1}$ (if the RBC is moving away from the probe).

Therefore, $W_2 = \frac{V_{US} -/(+)\ V_{RBC}}{f_1}$

$$f_2 = \frac{V_{US}}{W_2} = f_1\ \frac{V_{US}}{V_{US} -/(+)\ V_{RBC}} \quad \text{(from above equation) .....(vi)}$$

Therefore, $f_1 = f_2 \frac{V_{US} -/(+) V_{RBC}}{V_{US}}$ .....(vii)

Combining equations (v) and (vii),

$$f_2 \frac{(V_{US} -/(+) V_{RBC})}{V_{US}} = f_o \frac{(V_{US} -/(+) V_{RBC})}{V_{US}}$$

Therefore, $f_2 = f_o \frac{(V_{US} +/(-) V_{RBC})}{(V_{US} -/(+) V_{RBC})}$ ..... (viii)

Let $f = f_2 - f_o$ = the frequency shift.

Using equation viii), $f = f_o \frac{(V_{US} +/(-) V_{RBC})}{(V_{US} -/(+) V_{RBC})} - f_o$

Therefore, $$f = f_o \left[\frac{V_{US} +/(-) V_{RBC}}{V_{US} -/(+) V_{RBC}} - 1 \right]$$

$$= f_o \frac{(V_{US} +/(-) V_{RBC} - V_{US} +/(-) V_{RBC})}{(V_{US} - V_{RBC})}$$

$$= f_o \frac{+/(-) 2 V_{RBC}}{V_{US} - V_{RBC}}$$

Given that V_{RBC} (usually no more than 4m/s) <<< V_{US} (1540m/s),

$$f \cong f_o \frac{(\pm 2 V_{RBC})}{V_{US}} = \pm 2 f_o \frac{V_{RBC}}{V_{US}}$$

The above simplifies to the final equation below when using U/S of 2 MHz frequency because V_{US} is a constant and f_o is determined by the U/S frequency (13):

$$\boxed{V_{RBC} = 0.039 \times f}$$ .....(ix)

Again "+" is used in the equation for a RBC moving toward the probe whereas "-" is used for motion opposite to this. There are two assumptions inherent to the above derivation:

1) A single object, in this case a RBC, reflects a single Doppler-shifted frequency.
2) The RBC is traveling in line with the transmitted waves i.e. the angle between the U/S waves and the direction of blood flow is either 0° or 180°.

However in reality the scenario is more complex. The second assumption is addressed in section IV B iii) entitled "Confounding Factors". The first assumption is discussed below.

C) Sample Volume and Doppler Spectra

Flow velocities from blood vessels may be obtained by using either continuous-wave Doppler or pulsed Doppler (14). In the former, U/S is constantly emitted from a crystal source within the transmitter and the reflected waves are simultaneously accepted via a separate receiver . Such a design would make it unsuitable to selectively insonate specific vessels in the complex vascular anatomy at the base of the brain. In order to identify and measure blood flow in certain vessels, reflected waves from only pre-selected depths are analyzed. To accomplish this, *pulsed range-gated design* is utilized (1, 14). Coherent bursts of ultrasonic waves are sent out from the transmitter at certain frequencies called the pulse repetition frequency (PRF). The PRF is usually set at 5-10 kHz (11). The bursts of frequency-

shifted waves are reflected back from numerous structures in the waves' pathway at specific times that are proportional to their depth in the brain. By sampling the reflected waves at selected times, a window into a specific spatial region (called the *sample volume*) at a particular depth is obtained. The length of the transmitted burst of U/S and the duration of opening of the range-gate (both of which are usually set at about 13 μs (11)) determine the dimensions of this sample volume. The duration of the transmitted bursts and the time over which the receiving gate is open are usually made equal to optimize the signal-to-noise ratio (1). Hence the same probe can serve as the transmitter and the receiver. Range-gating averages signals received over the time interval for which it is open to get the *time-averaged means*. The highest and lowest values, corresponding to systolic and diastolic velocities, can also be recorded but it is usually the time-averaged means that are used clinically (12, 15). The internal carotid artery (ICA) bifurcation can usually be found at a depth of 5-6 cm, the proximal middle cerebral artery (MCA) at 3-5 cm and the A1 segment of the anterior cerebral artery (ACA) at 6-8 cm (12, 15, 16). The direction of flow can also be ascertained to aid vessel identification. For example the flow should be toward the probe in normal M1 but away in normal A1 segments.

Because the sample volume contains numerous RBC's and not just a single RBC as was assumed during the above mathematical derivation, a mixture of Doppler shifts containing many frequencies rather than a single, pure one will be obtained (the latter occurs when an embolus traverses the sample volume). The above Doppler shift, f, is perceived through the earphones of the Doppler machine and is represented by the outline displayed on the spectral analyzer. This can be converted into a

velocity value using *spectral analysis*. One such spectral display is shown in **Figure 1**.

D) Theory Behind the Use of TCD to Detect Vasospasm

The *equation of continuity* describes fluid flow through a pipe of non-uniform size (2, 9). There are several inherent assumptions:

1) The amount of flow (volume per unit time) is constant or in a steady state.
2) The fluid is incompressible. In other words its density stays constant.
3) The fluid cannot escape through the walls of the pipe.
4) Fluid flow is not turbulent, i.e. each element within it has an angular velocity of zero about its center.

Under the above conditions, based on the law of conservation of mass and constant flow,

$\Delta v / t = A V =$ constant, ...**(x)**, where $\Delta v / t$ is a sample volume of flow per unit time, A is the cross-sectional area of a particular segment of the pipe and V is the fluid velocity in that segment.

Hence, $A1\ V1 = A2\ V2$, where 1 and 2 are two segments of the pipe with differing cross-sectional areas. Since the cross-sectional area of a tube is πr^2 where r is the radius of the tube at that segment,

$$\pi (r1)^2\ V1 = \pi (r2)^2\ V2 \quad \text{or} \quad (r1)^2\ V1 = (r2)^2\ V \quad \text{.....(xi)}$$

Clearly pulsatile blood flow in situ through elastic semi-permeable vessels with branches does not fulfill all the above conditions. In addition, as will be

described in section IV B iii) below, the blood flow may not hold constant. Despite these caveats, the above *ideal fluid model* is still the simplest and clinically useful paradigm of intracranial arterial blood flow for the purposes of TCD studies. Thus if the flow through a vessel is held constant then any change in the fluid's velocity should mirror a change in its radius (from equation xi). Therefore if the radius decreases, as it does in vasospasm following subarachnoid hemorrhage (SAH), then the blood FV through the spastic segment should be higher than the velocity in the segment preceding or following the narrowing. This forms the premise upon which the use of TCD to diagnose cerebral vasospasm is founded.

E) Normal and Abnormal Values

The mean MCA velocity is approximately 58-65 cm/s with a standard deviation of 8-17 cm/s and the range is 30-90 cm/s. The mean ACA velocity is approximately 47-58 cm/s with a standard deviation of 9-15 and a range of 30-70 cm/s (8, 17, 18). The mean posterior cerebral artery (PCA) velocity is approximately 42- 44 $\pm$ 10-13 cm/s with a range of 30-70 cm/s (8, 17, 19). The TCD criterion for diagnosing vasospasm of the MCA is considered by most to be 120 cm/s (20-24) with the likelihood of spasm rising as the flow velocity increases. This criterion is not unanimously agreed upon as will be seen in section VIII below. Significant spasm is highly probable at FV > 200 cm/s (25-28).

III. Anatomical Considerations During TCD Examination

Despite the relatively low frequency used for TCD analysis, it is not possible to penetrate most parts of the skull because the bony spicules in cancellous bone cause considerable scattering of the U/S (14). Therefore certain natural foramina and the thinnest portions of the skull, called *acoustical windows*, are used to access the intracranial vasculature (29, 30). There are three such windows:

1) The **transtemporal window**, described in 1982 by Aaslid, uses the squamous portion of the temporal bone superior to the zygomatic arch and anterior to the ear. The diploe being absent here, it constitutes the thinnest portion of the skull. Even then the bone absorbs at least 65% of the ultrasonic energy (14). This is the most frequently utilized route as the MCA, ACA, intracranial ICA (IC-ICA), proximal PCA, and the posterior communicating artery (PCoA) can be explored. This is depicted in figure 2.
2) The **transorbital window** was described in 1986 (31). The probe is applied over closed eyes and U/S of approximately 5 MHz frequency is transmitted to compensate for the thin orbital walls and to reduce ultrasonic exposure to the globe. The cavernous and supraclinoid ICA as well as ophthalmic artery can be assessed (figure 3). Reversed flow (away from the orbit) in the ophthalmic artery is abnormal and alerts the examiner to collateral flow to the hemisphere suggesting significant stenosis or occlusion in the intra- or extracranial ICA (EC-ICA) (30, 32).

3) The **transforaminal window** (figure 4 on page 39) takes advantage of the foramen magnum to evaluate the vertebral (VA) and basilar (BA) arteries and occasionally the posterior inferior cerebellar artery (PICA). The patient is required to flex the neck to accentuate the space between the opisthion and the atlas (12, 30). It is however difficult to reliably identify the VA and the BA, partly because of the difficulty in distinguishing these vessels from the anterior inferior cerebellar artery, the PICA, and the superior cerebellar artery.

Sometimes fortuitously a burr hole located favorably over a specific blood vessel (e.g. a frontal burr hole in proximity to the ACA) can be used (29, 33). In general, the desired vessel is identified using a combination of strategies. The direction of flow, strength of signal, determination of the spatial relationship of the signal with other known arteries, characteristics of the signal at various depths, and response to compression or vibration maneuvers can all be helpful (14, 34). Since the actual vessel cannot be visualized, this is essentially a "blind" procedure. Small, frequent adjustments in transducer position ensure the smallest angle, ideally 0° or 180°, between the vessel and the ultrasonic beam. This is elaborated on in the section "Confounding Factors" (section IV B iii) below. As can be appreciated, performing a TCD study accurately and consistently, requires training, skill, experience and patience.

IV. Advantages and Drawbacks of TCD

A) Advantages

In 1951 Ecker and Riemenschneider reported:

> "It is probable that arterial spasm plays an important role following spontaneous rupture of saccular aneurisms of or near the circle of Willis" (35).

They first drew the attention of the medical community to what has become one of the most significant and intensely studied complications of SAH. They correctly postulated that

> "excessive spasm may produce unfavorable effects by impairing the circulation of the brain…" (35).

As new and more effective therapies for treating vasospasm have emerged over the years, the accurate and timely diagnosis of this phenomenon has become increasingly important (36-42). Until 1982 cerebral angiography was the sole tool at the clinician's disposal for diagnosing and following cerebral vasospasm. However angiography is invasive, associated with significant complications in 0.5% – 1% of cases, impractical to perform repeatedly, time consuming and taxing on resources. In contrast, TCD is non-invasive, safe, and can be repeated as required to diagnose or follow the course of vasospasm. The machine is portable to the bedside thereby precluding the need to transport a potentially unstable patient. Each study is relatively inexpensive. Compared to the luminal narrowing observed on an

angiogram, FV can provide a more direct reflection of the alterations in hemodynamics resulting from vasospasm or other causes.

B) Drawbacks

These can be grouped into technical, anatomical and confounding factors:

i) *Technical Factors*

As mentioned in Section III, the performance of TCD requires skilled personnel who have received training and are dedicated to its use (10). Obtaining valid results demands experience in identifying the desired vessel by optimizing the sample gate depth to segregate the various sources of TCD signals. Aligning the transducer with the vessel axially optimizes the signal which can then be converted into the highest velocities. The real blood FV is related to the observed velocity as follows (1):

$$V_{real} = \frac{k}{\cos\theta} V_{obs} \quad \text{.....(xii)},$$

where θ is the angle between the ultrasound and the path of the blood flow or vessel, and is a constant.

Therefore the observed velocity will correspond exactly to the actual velocity only when $\cos\theta \doteq 1$ or -1 i.e. when $\theta = 0°$ or $180°$ and that is why the TCD transducer should be as parallel as possible to the vessel. At an angle of 30° (or 150°) the observed velocity is approximately 87% of the real velocity and this is generally regarded as the upper limit of acceptable error (26). As one moves away from 0°/180° to 90°, the discrepancy mounts substantially. Hence the true velocity will always be either equal to, or more commonly, higher than the observed velocity. According to Fujioka and Douville,

> "the most significant challenge … is achieving accurate vessel identification" and "the primary deterrent …aside from a lack of operator experience is the enormous anatomical variance in the configuration of the Circle of Willis …" (29).

To ensure adequate practice, a relatively large volume of such studies must be performed (43). The accuracy of TCD values can therefore be, to a certain extent, operator and institution dependent.

Another technical factor that can impede a proper examination is the inability of U/S to penetrate thick bone. This presents an obstacle in 5-15% (44-46) of patients, but can occur in 3% (47) to as many as 26% (48) of patients. It is most common in elderly females (30). Certain races (especially African American) may show a predilection for prohibitively thick temporal bones (48). A craniotomy incision can also complicate the study. Incisional staples (but not sutures) coinciding with the location of the acoustical window can interfere with U/S transmission (29). Soft tissue swelling may add 2 cm or more to the vessel depth and can therefore confuse the recognition of the desired vessel.

ii) *Anatomical Factors*

The MCA is the only vessel amenable to a Doppler examination for FV using the standard techniques (20, 49, 50). There are several reasons for this. The proximal MCA, which is the segment most commonly involved in vasospasm, runs horizontally in a posterolateral direction from the ICA bifurcation. Hence the θ angle at the transtemporal window is relatively close to 0°. Furthermore, the MCA is

considered to be an end artery due to little collateralization and therefore the FV in this vessel most closely reflects the actual blood flow "seen" by the tissue in its territory. It also carries the majority of the blood flow to the hemisphere.

The oblique course of the distal IC-ICA, PCA, PCoA and ACA make these vessels unsuitable for extracting meaningful inferences from their FV, if they are found (20, 33, 49, 51). The ACA can derive most or all of its blood supply from its contralateral counterpart through the anterior communicating artery (ACoA). The A1 segment may be hypoplastic unilaterally. Hence elevated or decreased velocities in this artery cannot be depended upon to provide useful information (33). Not surprisingly, the sensitivity for detecting vasospasm in this artery has been found to be as low as 18% (51) and the correlation coefficient between ACA diameter and vasospasm diagnosed by TCD has been reported to be in the -0.25 (52, 53) to < -0.3 range (25). Lindegaard has suggested that for the proximal ACA's both should be considered together rather than separately because

> "in unilateral ACA spasm, …its FV will depend upon the state of the ACoA" and "the situation most important clinically is when ACA FV is high bilaterally, indicating bilateral ACA spasm or an inadequate ACoA" (17).

This strategy remains to be validated in clinical studies.

Regarding the intracranial ICA, Burch et al. reported a specificity of 93%, but sensitivity of only 25%. There was poor correlation between the degree of stenosis and velocity (r = 0.136) (54). The PCA does not fare much better. The common anatomic variation of fetal origin of the PCA (in 15% - 20% of patients) adds to the

difficulty. Wozniak et al. reported a sensitivity of 48% in the PCA (51). Lindegaard however reported a correlation coefficient of 0.68 between PCA angiographic vasospasm (AV) and FV (55). As stated previously, differentiating between the major arteries of the vertebrobasilar system poses a challenge. Using angiography as the gold standard for patients presenting with acute ischemic events, the positive predictive value (PPV) of TCD for detecting stenosis in the posterior circulation was 25% (48). In general, the role of conventional TCD (as opposed to TCCD) currently in evaluating stenosis of the posterior circulation is at best dubious (16, 56, 57).

The sensitivity of this instrument depends not only on the specific artery involved but also on the distribution of vasospasm in an arterial tree. Distal blood vessels are beyond the reach of TCD. It can consistently probe only the proximal segments of the MCA, ACA and PCA through the usual acoustic windows (12, 25, 33). Although exclusively distal vessel spasm is uncommon (28) and occurs in only 7.5-10% of cases (21, 58), this can produce a false negative result.

Space occupying lesions such as hematomas in the vicinity of vessels being insonated can add to the complexity of interpreting TCD values. Sufficient distortion of the vessel's course or alteration of the insonation angle can produce misleading FVs. Another anatomical factor to be wary of is marked stenosis proximal to the Circle of Willis. This usually affects the distal IC-ICA or EC-ICA, the latter due to atherosclerotic disease. This can reduce flow and hence the velocity in the basal vessels, thereby potentially masking significant stenosis of the basal cerebral arteries (59). Rorick et al. found this to be "the most important confounding factor" in their

study of intracranial stenosis in patients presenting with "acute cerebral ischemia" (48). Finally one must consider constriction of the cerebral arteries that is severe enough to cause low TCD velocities due to dramatically compromised blood flow. Alternatively in such an event the U/S signal may be too weak to accurately quantify any velocity at all (12). Such a case would doubtless be evident on an angiogram but can be missed by TCD.

iii) *Confounding Factors*

The observed blood FV in any artery is dependent on two variables: the blood flow in that vessel and the radius. Recall that the *observed* velocity is related to the *actual* velocity through cos θ (equation xii). The equation below describes the relationship between the observed blood FV, the blood flow, and the radius (52, 60, 61):

$V = \frac{CBF}{\Pi r^2}$ ..... **(xiii),** where CBF is the cerebral blood flow and r is the vessel radius.

To neurosurgeons the current main purpose of TCD is to serve as an early warning device for developing cerebral vasospasm, to diagnose it once established, to predict its clinical sequelae and to follow the luminal narrowing to its resolution. Other applications of this tool are outlined in the next section. In most cases the clinician seeks an estimate of any vessel narrowing based on the TCD results. A link with any ensuing ischemic deficits also would be ideal but this is more indirect and usually weaker as will be discussed later. Hence if one is interested in evaluating the "r" given the "V" in the equation, it follows that the CBF must be held constant.

However there are a number of conditions that can influence the CBF to a particular region. Other entities besides vasospasm can modify arterial diameter. Together they comprise confounding factors that may restrict the predictive value of TCD in the management of vasospasm following SAH (43, 62).

A significant insult such as trauma, SAH, or ischemia impairs cerebral autoregulation (63-65). The cerebral circulation then becomes passively dependent on the systemic circulation (66). In fixed cerebral arterial spasm the CBF can be more easily affected (67-69) by factors pointed out by Poiseuille's law (9) as the vessel radius is resistant to respond appropriately to physiologic influences:

$$F = \frac{\Pi (\Delta P) r^4}{8 (L) (I)} \quad \text{..... (xiv),}$$

where F = fluid flow in a tube, ΔP is the pressure differential across the tube, r is the tube's radius, L is its length and I the fluid's viscosity.

Hence cerebral perfusion pressure (CPP), and therefore intracranial pressure (ICP) and mean arterial pressure, can influence TCD velocities (43, 70, 71) by affecting the CBF. Flow can similarly be altered by blood viscosity, which is primarily determined by the hemoglobin. CBF has also been reported to vary directly with the patient's volume status (43, 70, 71), blood pressure (64, 72), reduced hematocrit (73, 74), pulsatility (75, 76), and cardiac output (69, 76-78), or a combination of these (79, 80). It is therefore generally believed that hyperdynamic therapy (HT) or the '3-H therapy' typically consisting of **h**ypervolemia, **h**ypertension, and **h**emodilution, ameliorates delayed ischemic neurologic deficit (DIND) or symptomatic vasospasm, by improving cerebral blood flow and oxygenation. The exact mechanism is unclear as discrepant data has been published (65, 81, 82). This is

further evidenced by the uncertainty regarding the relative contributions of the various variables to promoting CBF (83, 84). CBF may also fluctuate in response to local cerebral metabolic demands. Thus HT and increased CBF may artificially elevate TCD velocities thereby serving as potential confounders (16, 21, 85, 86).

In addition to vasospasm, the arterial radius (the second variable determining velocity in equation xii) is also subject to modification by arterial $PaCO_2$ or by compression from mass lesions such as a hematoma. The basal vessels are spared from the effects of $PaCO_2$ but the distal vasculature is susceptible and this can impact upon the ΔP and hence CBF in the equation. Other factors that some have associated with a higher FV include the female sex (55, 56), the side of the craniotomy (44, 87, 88), a younger age (11, 13, 16, 23, 34, 50, 55, 56, 89, 90) and the lack of a history of hypertension (91). The above factors do not appear to significantly influence the clinical interpretation of TCD results; their value is controversial as suggested by numerous opposing views (15, 18, 19, 23, 92) although the evidence implicating the effect of age is substantial and the influence of age is most likely real. Clinical grade on admission (88, 93, 94) and the amount of SAH (28, 44, 88) also have been positively correlated with FV but the accompanying hemodynamic changes are probably the underlying reason. The notion of the admission clinical status independently affecting TCD values has also been challenged (49, 53, 92).

V. Applications

Since Aaslid described the TCD as being "of particular value for the detection of vasospasm following SAH..." and useful "in the general handling of these patients" (8), TCD has gradually become part of the neurosurgeon's armamentarium for the management SAH patients (95, 96). The commonest indication for TCD has changed little over the past fifteen years, however many new uses have gradually emerged. These are briefly discussed below.

A) Ischemic Stroke

TCD can be useful in the initial evaluation of patients presenting with acute ischemic stroke (97, 98), to suggest the mechanism of the stroke and to provide prognostic information (21, 45, 46). It may help in the selection of appropriate patients for angiography (46). It may also allow the detection of spontaneous or thrombolytic-induced recanalization of a thrombosed vessel (30, 46, 57, 99). Alexandrov et al. characterized the type of perfusion patterns in 75 patients presenting with an ischemic event; 70% of the stroke patients had MCA occlusion or stenosis (45). TCD has also been used to uncover intracardiac shunts by detecting the passage of air bubbles (100, 101). At present TCD ultrasonography complements rather than replaces other modalities such as CT, MRI, MRA, and angiography. In the setting of acute ischemic cerebrovascular accidents (CVA) and transient ischemic attacks, TCD's influence on management and outcome is not yet established (57, 101, 102). New innovations such as TCCD hold promise for the future (103).

B) Intraoperative Monitoring During Carotid Endarterectomy (CEA)

The primary cerebrovascular complications of CEA intraoperatively result from either cross-clamping of the cervical ICA causing distal ischemia due to the inadequacy of the collateral circulation (104), or more commonly from emboli released from the endarterectomy site. TCD has been used to detect reduced ipsilateral MCA flow and to monitor for emboli during CEA (105-109). The significance of the observed changes is unclear. This is partly due to the absence of an accepted velocity threshold indicating tissue ischemia (104). Also TCD is not able to qualify or quantify emboli. According to a recent a consensus statement by leading experts, TCD currently lacks the required sensitivity and specificity for clinical detection of microemboli (110). In a study of 130 patients undergoing CEAs, 7 patients who demonstrated ≥ 70% reduction of MCA FV did not undergo shunting but only 1 suffered a stroke; the only other stroke occurred in a patient with normal FVs (108). Thus the value of intraoperative TCD in improving the outcome by its general use during all CEAs has not been established. In a study of 49 patients who underwent pre- and intraoperative Doppler examination, Bass et al. concluded that it "failed to provide information that altered surgical therapy" (107). Anecdotal reports attest to its benefit in individual patients (111). In general its benefit in carotid surgery is currently uncertain.

C) Other

Intracranial circulatory arrest determined by TCD can serve as an additional criterion to confirm brain death (30, 43, 46). Certain patterns such as reversed

diastolic flow or to-and-fro flow are highly specific to brain death (112, 113). However TCD findings during a transient ICP plateau wave may mimic those of brain death. TCD is insufficient by itself to diagnose brain death due to the numerous pitfalls alluded to earlier.

A further use of TCD can be found in determining the autoregulatory status of the cerebral vasculature in order to obtain prognostic information following various insults to the brain such as head injury (43). The clinical value of such an investigation is unclear at this time.

VI. Validity of TCD Velocities

Although cerebral angiography continues to be the gold standard for the radiographic diagnosis of vasospasm, the advent of TCD has been an important development in vasospasm detection and management. Several authors have reported the use of TCD to help plan surgery for aneurysmal SAH (28, 55, 88, 94). Others have used FVs, without angiographic confirmation of suspected vasospasm, to administer HT (28, 44, 52, 88, 114-118). Wardlaw et al. base the "timing and rate of mobilization and discharge" of patients on TCD velocities (118). Some investigators advocate completely replacing angiography with TCD for definitive vasospasm diagnosis (22, 25, 26, 33, 44, 55). An absolute prerequisite that must underlie all such recommendations is the presence of a significant and clinically useful correlation between transcranial Doppler velocities, the results of cerebral angiography, the hemodynamic consequences of vasospasm, and any resulting

neurologic deficit(s). Hence if one is going to allow TCD findings to guide decisions regarding potentially dangerous and possibly unnecessary interventions then the evidence linking Doppler FVs with angiographic vasospasm, CBF and delayed ischemic neurologic deficit (DIND) must be critically appraised.

A) Correlation between TCD and angiographic vasospasm

Aaslid et al. were the first group to report a correlation between the FV and angiographic vessel diameter (25). Since then others have corroborated their findings (20, 44, 52, 55, 60, 92, 118). The magnitude of this relationship has however varied considerably from correlation coefficient (r) of –0.47 (60) to –0.91 (60). Using a TCD definition of spasm as being >120 cm/s, the sensitivity of the technique at centers reporting a correlation has ranged from 85% (60) to 100% (118). The specificity has been as high as 100% (20, 118). Some have reported a high positive and negative predictive value of the test but no correlation with the severity of spasm (92). In contrast, several investigators discovered a poor relationship between the two parameters (15, 53, 54). Sekhar et al. reported $r < 0.25$ (53) and Burch et al. discovered a low sensitivity of 38.5% using a TCD criterion of 120 cm/s (54). In patients presenting with CVA, Rother et al. found systolic velocities to be unsatisfactory in predicting MCA stenosis as determined by angiography (119). A noteworthy point regarding all the above studies is that in most of them, either only a minority of patients had undergone a follow-up or baseline angiogram *during the vasospasm risk interval* (days 4-21 post-SAH), or this information was not specified (92, 118). For example Lindegaard reported $r = -0.91$ but only 5/51 patients had an angiogram subsequent to the initial one (60, 92, 118).

Creissard et al. studied 40 patients who had angiograms (mostly post-operative) that demonstrated vasospasm; they determined the sensitivity and specificity of TCD to be 93% and 100% respectively, and concluded that "Doppler is an excellent tool to establish vasospasm diagnosis" in the M1 segment (20). Burch et al. also studied 49 patients with angiograms within the vasospasm interval and reported a sensitivity of 38.5% and failed to find any substantial connection between the severity of vasospasm and TCD; they did however find TCD to be highly specific (93.7%) (54).

Thus the results of most studies are based largely on the initial angiogram performed < 3 days post-SAH and not demonstrating any vasospasm. The correlations reported are between the normal variations in the MCA diameter of the population and TCD velocities. Investigations involving angiograms showing vasospasm have produced conflicting results. The current literature contains little evidence that TCD can reliably distinguish between angiographically *significant* (defined in the section "Angiographic findings" in chapter 2) versus *mild* and therefore less important vasospasm, which is the key question from the clinician's standpoint. The discrimination between degrees of spasm is essential for clinical decision making on an individual basis. Isolated correlation coefficients linking vessel diameter of often non-spastic vessels, to FV are especially unhelpful in this regard.

B) Correlation between TCD and DIND

There are some studies that demonstrate a relationship between TCD velocities and clinical deficits attributable to vasospasm, and at least as many that contradict these conclusions. It is necessary to consider the use of prophylactic HT and nimodipine in the patients when studying the above issue as the former may ameliorate or prevent DIND (79, 120-123) and the latter improves the neurological outcome (124-126). Ideally the hematocrit, blood pressure, and $PaCO_2$ should also be taken into account as they can affect the FVs and the neurologic status.

Kilic et al. (88), Pasqualin et al. (93), and Hutchison & Weir (15) found significantly different FVs in patients who experienced DIND compared to those who did not. All patients received nimodopine but only the last pair of authors administered prophylactic hypervolemia. Examination of their data reveals considerable overlap of TCD values between individual patients in the two categories. Pasqualin et al. used the FV corresponding to the time period of DIND onset and failed to uncover a difference between the velocities of those with "mild" versus "severe" deterioration. The other two groups of investigators used the highest velocities reached throughout the hospital stay, which could have been reached following the onset of DIND and hence attributable to the HT instituted as treatment. Sander and Klingelhofer showed that patients with lower time-averaged mean velocities tended to have better clinical outcome at six months following spontaneous SAH ($r = -0.59$) but the impact of clinical grade on admission was not taken into consideration (71). Similarly Seiler et al. found that patients with symptomatic vasospasm manifested higher velocities that rose earlier compared with those without

DIND, however their conclusion that the rise preceded the onset of DIND is not clear in their report (28) and prophylactic HT does not appear to have been given.

A recent study of patients who received nimodopine and prophylactic HT revealed no significant relationship between TCD velocities and symptomatic vasospasm after taking potential confounding variables such as hematocrit, $PaCO_2$ and blood pressure into account (85). FVs corresponding to the time of clinical findings, rather than the highest values throughout the patient's hospital stay, were used. The importance of distinguishing between the two TCD parameters is underscored by the results of Grosset et al. who failed to find a predictive value of TCD when using data prior to the onset of DIND; however they did find significantly higher velocities in those with DIND when the highest velocity ever recorded was used for the analysis (114). The first scenario is obviously more relevant for predicting clinically important vasospasm. Numerous authors using either the highest velocities prior to or at the time of DIND or throughout the patient's hospital stay have noted an absence of significant correlation between TCD and DIND (44, 49, 92, 127-129). Again most did not customarily administer HT prior to DIND.

Thus the evidence from the literature does not support a consistent benefit of TCD in anticipating hemodynamically significant vasospasm which would then allow appropriate therapy to be instituted in a timely fashion. It is important to note that even though overall the correlation is not strong enough to guide treatment on an individual basis, very high velocities of over 200 cm/s have been frequently associated with poor clinical status (25-28, 47). There can be exceptions to this rule

(49, 92, 128) but at the very least such high velocities should prompt the clinician to rule out vasospasm. There are several reasons why radiological suggestions of decreased blood supply may not correspond with clinical signs. First the basal cerebral arteries being conductance vessels, mild to moderate (up to 50%) vasospasm may not diminish cerebral blood flow (130). Secondly, dilatation of the distal resistance intraparenchymal vessels and a variable collateral supply may compensate for the deficiency. Spasm of more distal vessels may also account for some of these differences. The brain is supplied with about twice the amount of blood flow required for neuronal function thereby providing a large reserve that forgives some compromise of blood supply. Normal CBF is 50 cc/100 g brain tissue/minute at rest and ischemia occurs at flows less than 30 cc/100 g brain/min. Finally the metabolic demands of the tissue being perfused may not be uniform between cases, depending on the function of the tissue. Another explanation in cases where CBF has been measured is that focal ischemia may not be diagnosed as only hemispheric or regional values are usually obtained.

C) Correlation Between TCD and CBF

Compromise of the balance between the CBF and the demand that forms the common pathway through which the neurological consequences of vasospasm arise. From equation xiii above, one would predict a direct relationship between the velocity and CBF *if the vessel diameter remained constant.* In SAH patients exhibiting varying degrees of vasospasm the latter assumption does not necessarily

hold true because, based on **equation xiv**, the flow varies directly with the fourth power of the radius. As the CBF and the vessel's radius counter each other's influence on the velocity, the end result will depend on the balance between the two and this in turn depends on the many variables previously discussed. Consequently the magnitude and direction of change of velocity in response to CBF changes can be unpredictable. The literature generally indicates a poor correlation between FV and regional or hemispheric CBF (131). Meixensberger reported a correlation coefficient of 0.29 (132). Similarly Clyde et al. who administered prophylactic HT to their patients, obtained $r^2 = 0.056$. Inspection of their scatter plot confirms the lack of a significant relationship (85); in fact the mean TCD velocity was lower in patients with reduced CBF which is contrary to the response predicted by Archer (130). Bishop et al. studied MCA systolic flow velocities and hemispheric CBF in 17 patients with "cerebrovascular disease" and found a correlation coefficient of 0.424 when the absolute FV was used, but it was 0.85 when the change in systolic velocity and CBF in response to induced hypercapnia was used (133). They concluded: "the absolute velocity cannot be used as an indicator of CBF". More recently when Lee et al. (23) investigated "hemodynamically significant cerebral vasospasm" in patients with head injuries they discovered that out of 34 patients who had 42 MCA readings of 120 cm/s or greater along with a concurrent ipsilateral CBF measurement, 18% of them were associated with hyperemia in contrast to the pattern observed by Clyde et al. Of these 34 patients, 47% "had an elevated velocity that was never accompanied by low CBF" whereas "53% had at least one … concurrent low CBF". Hence it

appears that the theoretical concerns raised at the beginning of this section are borne out by the clinical evidence.

D) Alternative TCD Parameters

It is apparent from the above discussion that there are limitations to the use of absolute flow velocity measurements by TCD. In response to these shortcomings a number of other TCD parameters have been proposed:

i) *Lindegaard ratio* (LR)

Aaslid et al. first noted lower velocities in the cervical ICA compared to the intracranial vessels (8). They later discovered that the extracranial ICA velocities varied inversely with intracranial FVs and were lower in patients with cerebral vasospasm (26). Shortly thereafter Lindegaard et al. calculated the ratio of the MCA velocity to the EC-ICA velocity, also called the *hemispheric index* (17). The rationale behind this ratio is that a higher MCA velocity due to increased CBF rather than decreased vessel diameter should be matched by higher flow (and therefore higher velocity as spasm does not extend into the extracranial vasculature) more proximally in the circuit (i.e. distal cervical ICA). Hence the ratio should stay relatively constant. On the other hand higher intracranial absolute velocities secondary to spasm should decrease the flow, and therefore the velocities, in the cervical ICA because of increased resistance in the circuit distally. Hence the ratio should rise in this case. The ratio essentially attempts to isolate the effects of CBF from that of the radius on the velocity. The ratio is also less dependent on age (55,

90). Normal LR range for MCA is 1 - 2.5, the mean being 1.5 - 1.8, while LR > 3 suggests the presence of vasospasm and LR > 6 indicates *severe* spasm (23, 50, 55). Several favorable reports of this parameter have appeared (17, 21, 50, 55, 60, 90, 134). Conversely some authors have been less supportive of the LR and have contended that it did not substantially add to the value of absolute MCA FV (23, 52, 114, 117). Some centers do not use this parameter as it has not been validated for routine clinical use yet (118). In order to prospectively compare this parameter with absolute velocities at the University of Alberta Hospital, LR are currently being studied as of October 1997.

ii) *Spasm Index* (SI)

Recently Lee et al. distinguished between "hemodynamically significant" cerebral vasospasm and "vasospasm per se" in a study of head injured patients (23). The idea of SI is not a new one (135) but it was modified by the above authors into a ratio of FV (in MCA) to the hemispheric CBF_{15} derived by ^{133}Xe clearance technique. They found that patients with a high SI had a significantly poorer outcome. Even though only 56% of those with a high SI (defined as being greater than 3.4 and compared to 48% when MCA velocity alone was used) demonstrated a poor outcome, they felt that this parameter better discerned "hemodynamically significant" vasospasm from insignificant vasospasm as it was the former that impacted on outcome. They point out that the SI takes into account the CBF and hence the potentially misguiding effects of hyperemia. In another study of head injured patients Romner et al. acknowledged that

"it is not possible to differentiate between these two conditions (hyperemia vs. vasospasm) using TCD alone"

He added that complementary tests such as a SPECT scan was needed to assess the CBF in order to distinguish between the two entities (134). Although the above results cannot be directly applied to patients with aneurysmal SAH, the concept may prove to be relevant in this patient population as well.

iii) *Other*

Other TCD parameters have been proposed but their accuracy has been poor, inconsistent or unconfirmed. The rate of FV rise is one such measurement. Thresholds varying from 25 cm/s/day (26) to 50 cm/s/day (114, 128) and 50 cm/s/ 2 days have been advocated (118). Other authors have failed to find an increase in velocity to be a useful predictor of DIND (49, 136). Clyde et al. likewise found no correlation with changes in local CBF (85). Other suggested parameters include the difference between the initial velocity (on admission) and the highest recorded in a particular segment (88), and the FV difference between the two sides (11, 34, 48).

The concept of pulsatility (PI) and resistance indices (RI) (also known as the Gosling and Pourcelot indices respectively), are based on the interplay between the resistance and compliance of the cerebral vasculature (137).

$RI = \frac{V_s - V_d}{V_s}$ and $PI = \frac{V_s - V_d}{V_m}$, where "s" stands for systolic, "d" for diastolic and "m" for mean.

They represent variations of the same idea that the shape and amplitude of the velocity wave form on a spectral display are altered by vasoconstriction. They are dimensionless. The indices theoretically increase with vessel narrowing (137) but are dampened by proximal stenosis or distal vasodilation (91). These indices are not dependent on the angle of insonation. There are several disadvantages though. The changes in the indices can be small and easily overshadowed by other cardiovascular factors such as heart rate and rhythm, stroke volume, blood viscosity, and cerebral autoregulation and furthermore the measurements may not be readily reproducible (137, 138). Lindegaard states that "it seems difficult to estimate vascular resistance from PI analysis alone" (138). Several authors have demonstrated a poor correspondence with DIND or clinical outcome. Hence reliance on these TCD parameters is unjustified at this time (85, 93, 94, 127).

VII. New Developments in TCD Sonography

Since the early days of U/S more than four decades ago, advances such as the use of lower frequencies, pulsed range-gated design, and spectral analysis have enabled neurosurgeons to assess flow in intracranial vessels in a safe and non-invasive manner. In the current era of burgeoning technological innovations, continued progress in transcranial Doppler ultrasonography and its applications is inevitable. Spectral signal can now be recorded on magnetic tape or as a digital signal, offering the option of continuous monitoring, trend analyses using computers

and multi-channeled Doppler for continuous recording of more than one vessel (usually bilateral MCA's) simultaneously (43).

Transcranial *duplex* ultrasonography refers to the *double* display of both the spectral Doppler signal and the real-time (B-mode) black and white image of the echogenic brain structures (fig. 5 on page 40). This was first applied in the pediatric population about 9-10 years ago by Schoning et al. (Schoning et al. *cf.* Bartels et al. and Bogdahn et al.) (139, 140). Since then its use has been expanded to adults. In 1990 Bogdahn et al. introduced transcranial color-coded duplex (TCCD) real-time U/S which allowed for the first time the visual depiction of blood vessels and color-coded direction of blood flow in the context of black-and-white B-mode image of the surrounding parenchymal structures using U/S (140). Flow toward the transducer is depicted in red while flow away is represented in blue (fig. 6 on page 41). The shade of the color reflects FV. This innovation allows confident identification of the vessel in real-time, the measurement of the insonation angle and correction for it in order to obtain a value closer to the true velocity (56, 103, 139, 140). The latter advantage may prove especially beneficial because the angle varies greatly among individuals (139) and can be difficult to anticipate in the presence of local mass lesions. These new features come at a cost though, both monetary and technical. As a slightly higher U/S frequency of 2.25 MHz is used, reduced penetration through an acoustical window may result with as many as 23%-30% of people proving to be completely resistant to U/S penetration (56, 141). This technique remains to be validated in the setting of cerebral vasospasm. Categorical acceptance of TCCD's superiority over TCD for this indication should be avoided for the following reasons:

1) Schoning et al. found that TCCD values were simply "shifted upward parallel to the TCD series by a factor that corresponds largely to the angle correction" (18). Hence if consistency in personnel and technique is maintained for a particular patient then the importance of the trend overshadows that of the absolute relationship between the observed velocity and the true velocity. Indeed the authors felt that

   "the advantage of the TCCD is associated more with the qualitative aspect than a quantitative one".

2) The numerous and frequently fluctuating confounding variables previously described are probably to be blamed more than the insonation angle for unreliable TCD velocities in a given patient. The former issue remains unaddressed by TCCD.

3) Laumer et al. used 3-dimensional TCD and failed to find a correlation between FV and DIND (49).

4) There is no data currently that indicates an improved ability of TCCD to presage, diagnose or monitor vasospasm when compared to conventional TCD.

However the enormous potential of this technique is obvious. Newer generations of TCCD machines can measure the actual vessel size, thus combining the advantages of the TCD with those of the angiogram. Visual confirmation of vessel identity can grant better access to cerebral arteries previously sheltered from conventional TCD (e.g. PCoA) (27). Baumgartner et al. showed that venous structures can now be insonated using TCCD (142). The most recent advance in this field within the last three years is the power-based TCCD which was designed to

improve the signal-to-noise ratio and limit the sources of error that plague the commonly used frequency-based TCCD. No notable advantages were found (143).

Over the last 3-4 years contrast enhanced TCCD has been introduced to the clinical arena (144, 145). The contrast enhancers strive to improve the resolution and widen the spectrum of intracranial pathology that can be imaged using U/S (146). They use air-filled microspheres of albumin or galactose-derived microparticles. They also allow access to the peripheral branches of cerebral arteries, hitherto impossible using unenhanced ultrasound (145). Cerebral sinuses are more accessible using this technology. Furthermore they augment Doppler signals in patients whose skulls may be strongly attenuating and otherwise immune to U/S (147). The FV values themselves are generally unchanged compared to unenhanced sonography (146).

Bailes et al. recently reported the use of intraoperative microvascular Doppler sonography in aneursym surgery to successfully document the status of the parent artery and perforating vessels, and to guide clip adjustment if necessary to ensure their patency (148). Given its non-invasive nature and the time saved compared to intraoperative angiography, if detection of residual aneurysm necks could be achieved, it could obviate the need for intraoperative angiography. Recently detailed attempts at estimating ICP and CPP on a continuous basis using TCD provide hope for a noninvasive means of measuring these parameters one day; this technology is still in its infancy at present (149).

VIII. Conclusions

There is ample evidence in the literature for a role for TCD in the diagnosis and management for cerebral vasospasm following aneurysmal subarachnoid hemorrhage. The precise nature of this role is however controversial. The various technical and anatomical factors, and the wide array of potential confounding variables that can impact on FV explain the frequently contradictory data in the literature. This is reflected in the lack of a consensus on the TCD definition of vasospasm (17, 21, 48, 54, 92, 115, 118, 150) which ranges from 80 cm/s (48) to 140 cm/s (150) and even 155 cm/s (for DIND) (53). Brint et al. consider the sum of bilateral MCA velocities exceeding 180 cm/s as their threshold for diagnosing vasospasm (87). Such discrepancy contrasts with the striking similarity of normal TCD reference values in the literature (8, 11, 13, 18, 34, 90).

Recently numerous authors have questioned TCD's dependability and clinical usefulness in individual patients (20, 49, 53, 54, 85, 89, 93, 128). Based on the current literature, the only concrete statement that one can safely make regarding the use of TCD FV is that very low values such as <100-120 cm/s are seldom associated with significant cerebral vasospasm whereas very high values (>200 cm/s) should evoke strong suspicions of significant vasospasm. A large proportion, if not the majority, of patients however fall in the 'grey zone' in between where the predictive value of TCD declines markedly. It is therefore imperative for any neurosurgical center using TCD to assess vasospasm, to scrutinize its own experiences with this tool and to objectively evaluate its merits and limitations.

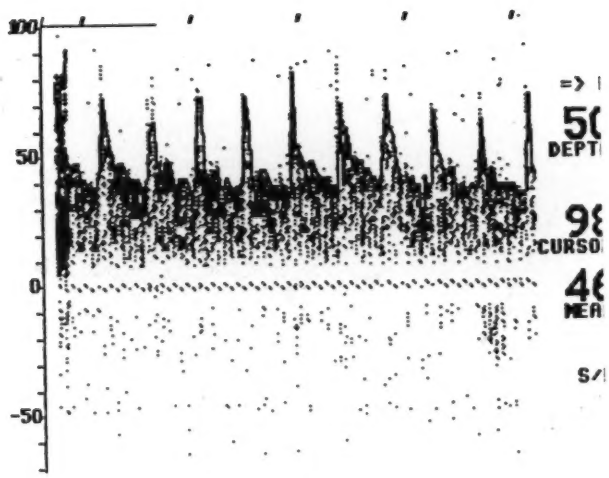


Figure 1: TCD spectral tracing of the right MCA in a SAH patient. The vertical axis on the left denotes the blood FV in cm/s.

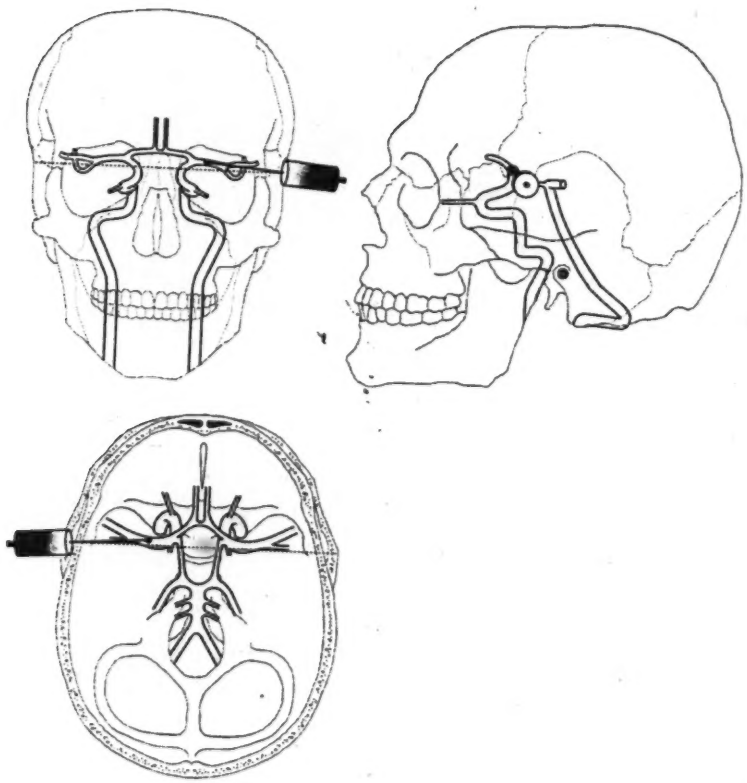


Figure 2: Anteroposterior, lateral and cross-sectional views of the transtemporal acoustical window (29).

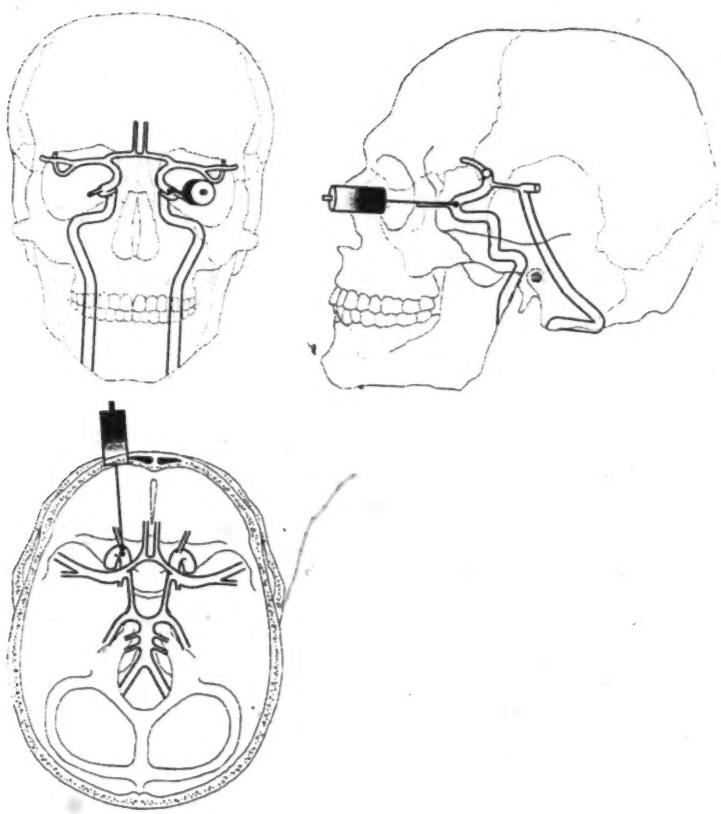


Figure3: Anteroposterior, lateral and cross-sectional views of the transorbital acoustical window (29).

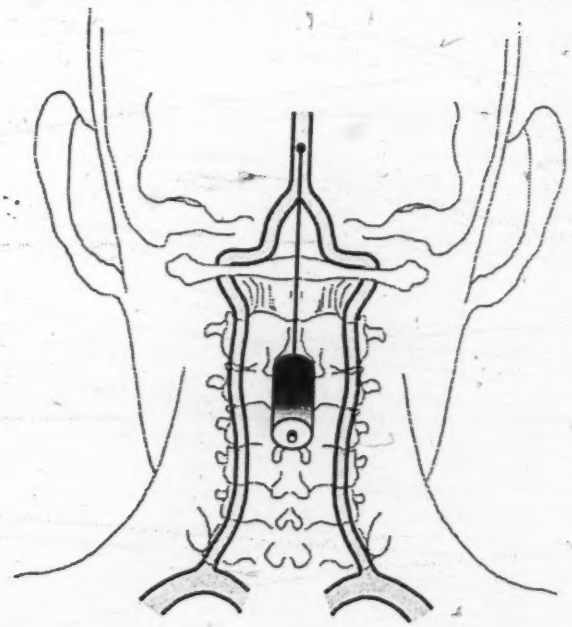


Figure 4: Posterior view of the transforaminal acoustical window (29).

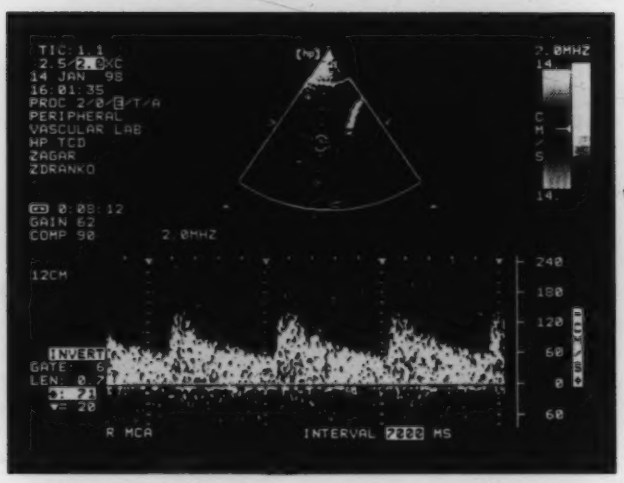


Figure 5: Transcranial duplex image. The B-mode black and white image of the brain parenchyma is shown in the top part and the spectral velocity display is shown in the bottom. The vertical axis on the bottom right marks the blood FV in cm/s.

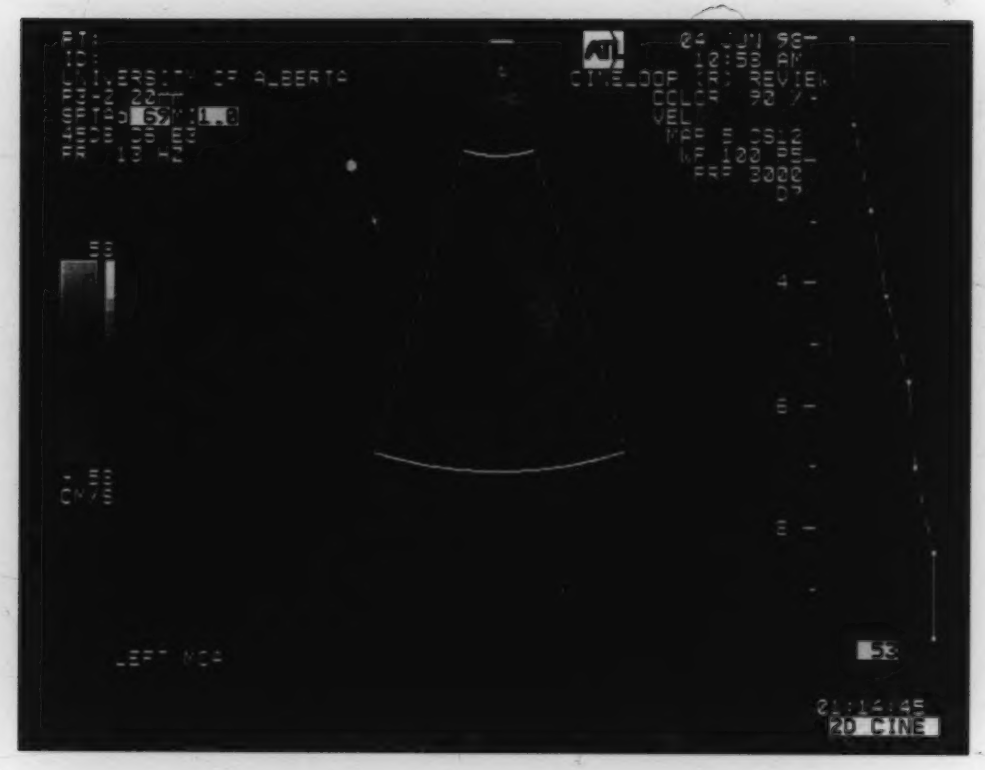


Figure 6: Transcranial color-coded duplex image of a normal right MCA. Red color denotes flow toward the probe situated at the apex of the picture at the top, and blue denotes flow away from the probe. The shade of the color reflects the velocity as specified on the left side along the vertical color bar.

OBJECTIVES

1) The primary goal of this study is to determine the correlation between absolute TCD velocities and angiographic cerebral vasospasm by determining the predictive value of the velocities for diagnosing angiographic vasospasm in the middle cerebral artery (MCA), following aneurysmal SAH. As an extension of the above objective, the correlation between Lindegaard ratios and angiographic vasospasm is also to be determined.
2) There are several secondary objectives as follows:
   a) To evaluate the correlation between absolute TCD velocities as well as Lindegaard ratios, and DIND.
   b) To evaluate the correlation between angiographic vasospasm and DIND.
   c) To elucidate the influence of hyperdynamic therapy on TCD velocities.
   d) To assess the influence of the amount of SAH as seen on the initial CT scan, on angiographic vasospasm.

HYPOTHESIS

Low (< 120 cm/s) and high TCD velocities (≥ 200 cm/s) correlate well with angiographic vasospasm. Lindegaard ratios will correlate better with angiographic vasospasm than absolute velocities.

CHAPTER 2: MATERIALS AND METHODS

Patient Population and Study Design

This study consists of two parts. Part I involves a retrospective review of patients between Jan 1994 – May 1997 in order to evaluate the value of absolute velocities. Lindegaard ratios were not performed at the University of Alberta during this interval. In part II, the predictive value of Lindegaard ratios is evaluated in a prospective manner between Oct 1997 and Apr 1998.

PART I

Patients admitted to the University of Alberta Hospital and diagnosed with aneurysmal SAH between Jan 1, 1994 and May 31, 1997 were identified using the discharge diagnosis listings in the department of Medical Records as well as the TCD logbook containing a list of the patients who have undergone TCD examination. The latter source was used because TCD exams are routinely performed on all aneurysmal SAH patients admitted to this hospital. The inclusion criterion consisted of admission with a SAH from a ruptured intracranial aneurysm. Patients were excluded if an angiogram during the vasospasm risk interval (days 4 – 21 post-SAH) was not performed or if at least one TCD exam prior to or within 1 day of the follow-up (f/u) angiogram was not conducted. Patients who were moribund on admission such that

they were not actively investigated or treated, were not considered for this study. A retrospective review was carried out to collect the data specified below.

Data Recorded for part I

The data collected can be classified into several categories: patient demographics, putative determinants / predictors of cerebral vasospasm, relevant past history, various TCD velocity parameters, the day of the f/u angiogram and its findings of cerebral vasospasm, extraneous variables that may potentially influence TCD velocities, and evidence of DIND.

Patient Demographics

Patient age, sex, admission day post SAH (day 0 was defined as the day of the initial bleed) and the day of definitive treatment post SAH were noted.

Vasospasm Risk Factors / Predictors

The WFNS (World Federation of Neurological Surgeons) clinical grade on admission and the thickness subarachnoid blood clot in the basal cisterns and the interhemispheric and both Sylvian fissures on the admission non-contrast CT scan of the brain were recorded. CT scans were assessed only if the admission was within 2 days of the SAH. Clot thickness and was dichotomized as "thick" or "thin" based on a visual assessment of the density and width of the clot evident on the single cut of the CT scan that demonstrated the most blood. This method of determining clot thickness has been previously employed (151). Examples of thin and thick clot are

shown in **Figures 7 and 8** respectively. Tissue plasminogen activator (TPA) or papaverine were sometimes instilled in the basal cisterns intraoperatively. In some cases TPA was injected into the lateral ventricles post-operatively depending on the severity of intraventricular hemorrhage. This too was documented.

TCD parameters

The TECA TC 2-64 transcranial Doppler machine by EME, Eden Medizinische manufactured in Germany was used to measure intracranial blood flow velocities. The maximum time-averaged mean flow velocity in the M1 segment of the MCA was obtained at 3 depths between 4.5 to 6.5 cm, each measured at 0.5 cm intervals, usually at 5, 5.5 and 6 cm. The deepest site corresponded to the proximal segment of M1. The following parameters for both the right and left sides were recorded: highest velocity throughout hospital stay, highest velocity prior to the f/u angiogram including on the day of the angiogram, velocity within 1 day of the angiogram (this was almost always on the day of the angiogram), the largest right – left difference between corresponding segments within 1 day of the angiogram and the highest velocity attained during hyperdynamic therapy (defined below) and during no hyperdynamic therapy (HT) in the same patient. The highest TCD value during hyperdynamic therapy was chosen with attention to the time of day of TCD in relation to the time of day that HT was first and last administered.

Values obtained *prior to* (including the day of) the f/u angiogram for the following parameters were also noted for both sides: largest 1 day velocity rise in the same M1 segment, largest velocity difference over any 2 days in the same segment,

and among any of the 3 M1 segments on the same side, number of consecutive days of velocity rise, and the largest right-left difference between analogous segments on the same day. The highest mean velocity obtained for each side during days 0-3, 4-6, 7-9, 10-12 and 13-16 post SAH were also recorded. In those patients who experienced DIND, the highest mean velocity reached prior to (including the day of diagnosis) DIND was recorded. Finally the total number of days each patient had a TCD examination was noted.

Angiographic findings

The baseline and f/u cerebral angiograms were gathered for 101 out of the 102 patients who had a f/u anterior circulation cerebral angiogram during the vasospasm risk time interval; for 1 out of the 102 patients the f/u angiogram films could not be located. Cerebral angiography was used as the "gold standard" for the diagnosis of vasospasm in this study. It was usually performed between days 7 and 10 post-SAH, independent of the TCD or clinical findings. Its main purpose was to confirm the exclusion of the aneurysm from the circulation with the added benefit of evaluation of any vasospasm that may be present. The angiograms were performed earlier if clinically indicated. In a minority of patients, CT angiograms instead of digital subtraction angiograms were performed on admission. In 5 patients baseline angiograms free of vasospasm were not available and hence only the f/u angiograms were assessed. At least 2 angiographic views were used (usually AP and oblique) to quantify the degree of vasospasm in the vast majority of patients. Two independent observers, both blinded to the identity of the patients and the TCD results, evaluated

the angiograms. Angiographic vasospasm was classified as follows: none, mild (narrowing < 1/3 of baseline luminal diameter), moderate (narrowing ≥ 1/3 but ≤ 1/2 compared to baseline) and severe (narrowing > 1/2 compared to baseline) for both sides. In case of any doubt regarding the vasospasm grade, measurements were made by outlining on a piece of paper the boundaries of the contrast visualized at the site of greatest narrowing and superimposing this on the baseline film at an analogous segment of the vessel. A micrometer and a magnifying device were not used because measurements thus obtained would not reflect clinical reality and would be impractical to reproduce during the day to day clinical management of SAH patients. Significantly discordant readings by the two observers (specifically disagreements between none/mild versus moderate/severe or moderate versus severe vasospasm) were resolved by consensus after the weighted kappa value for agreement beyond chance was calculated. None or mild vasospasm was defined as clinically "insignificant" and moderate or severe vasospasm was defined as clinically "significant" vasospasm. This was based on the common clinical experience that patients with narrowing between 1/3 to 1/2 of the orignal vessel size could experience DIND but those with slight or minimal narrowing of less than 1/3 the original diameter do not suffer ischemic deficits owing to diminished blood flow secondary to vasospasm. Luminal narrowing of greater than 1/2 was used to define "severe" vasospasm since a reduction in diameter of greater than 50% is considered to be associated with a significant decrease in blood flow (51, 152). Examples of the 4 grades of angiographic vasospasm are depicted in **Figure 9**.

Three vessels were evaluated on each side (hence a total of 6 / patient): the A1 segment of the ACA, the M1 segment of the MCA and the supraclinoid ICA. Moderate or severe distal spasm in the ACA or MCA that was not present in the above proximal portions was noted. In 3 patients f/u angiograms were performed on only one side. In addition, information for A1 was considered "unavailable" in a total of 6 sides either due to an aneurysm clip obscuring the view or because the artery was suspected to be hypoplastic but this could not be confirmed due to the absence of a baseline view. The day post SAH that the f/u angiogram was performed on was also recorded.

Extraneous variables that may also potentially influence TCD velocities

When available, the central venous pressure, arterial PCO_2, hematocrit, and mean arterial pressure on the day of the TCD reading "within 1 day of the angiogram" were recorded. The values closest to the time of the TCD recording were used. In addition, the use of hyperdynamic therapy (HT) in the form of colloid (albumin was the only colloid employed) or inotropes / vasopressors was also noted. It was defined as the use of albumin bid or more frequently for 2 days or more, or the use of any inotropes or pressors, for the purpose of maintaining a state of hypervolemia or hypertension and not for the purpose of hemodynamic instability such as during hypotension. The number of days that albumin or inotropes / vasopressors were each used was recorded. Indications for HT included prophylaxis as well as treatment of asymptomatic or symptomatic vasospasm.

DIND

Symptomatic vasospasm was considered to have been present if it was diagnosed during the patient's hospital stay and retrospective diagnosis based on patient deterioration in the absence of any other obvious explanation was not attempted if the diagnosis was not established by the clinicians caring for the patient at that time. DIND is diagnosed at this institution based on the new onset of global or focal neurological deterioration after day 3 post-SAH and beyond 24 hours after surgery if not explained by other causes such as hydrocephalus, hemorrhage or infection.

PART II

The second part of this study prospectively evaluated the usefulness of Lindegaard ratios. All patients between October 01, 1997 and April 15, 1998 admitted with aneurysmal SAH were considered. The same inclusion and exclusion criteria as in part I were used.

Data recorded for part II

Patient demographics, clinical grade and angiographic findings were recorded similarly to the first part above. The use of HT, whether it consisted of fluids or inotropes / vasopressors was noted as in Part I of this study.

TCD parameters analyzed consisted of the Lindegaard ratio on each side of the patient obtained within 1 day of the angiogram and the highest Lindegaard ratio and time-averaged mean absolute velocity during normovolemic or hypervolemic therapy if the patient was part of the above mentioned randomized controlled study. The highest Lindegaard ratio during and during no HT was recorded for all patients as done for the absolute velocities in Part I of the study. Finally the highest Lindegaard ratio achieved on either side prior to the onset of DIND was compared to the highest Lindegaard ratio in those who did not develop DIND. The Lindegaard ratio was calculated as the ratio of the MCA velocity and the ipsilateral extracranial internal carotid artery velocity. For the purposes of this part of the study DIND was prospectively defined as follows:

A) The patient meets all of the following conditions concerning the neurological deficit or neurological worsening:

1. Onset after day 3 post-SAH.
2. Onset not within 24 hours of surgery.
3. Not explainable by presence of hydrocephalus, seizures, infection, raised ICP / cerebral edema, intracranial hematoma, medications, metabolic disturbances (including hypoxia, electrolytes, glucose, endocrine causes - e.g. hypothyroidism, uremia, hepatic encephalopathy).

AND

B) New onset of one or more neurological signs such as:

1. Decrease in GCS by 2 points or more.

2. Hemi / monoparesis, pronator drift, anosagnosia, hemineglect, all suggestive of middle cerebral arterial (MCA) insufficiency.
3. Dysphasia, also implying MCA insufficiency.
4. Poverty of speech / abulism / akinesia / mutism / paraparesis / frontal release signs, implying anterior cerebral arterial insufficiency.
5. Dysarthria, ataxia, vertigo, lower cranial nerve palsies, signs of cerebellar dysfunction suggesting inadequate vertebrobasilar blood supply.

Statistical Analysis

Data was entered into a database using the Microsoft Access 97 program. Analysis was performed using the SPSS 6.1 statistical software program (SPSS Incorporated, Chicago, IL, USA). 2 x 2 tables were constructed to calculate a test's sensitivity (Se), specificity (Sp), PPV, NPV and likelihood ratios for positive and negative tests (LR+ and LR- respectively). The post-test probabilities for the presence of or absence of angiographic vasospasm were calculated by multiplying the likelihood ratios for positive and negative tests respectively, by the pre-test odds and then converting the odds to probabilities. The calculation of the above parameters is shown below and their significance is addressed in the early part of "Discussion" (chapter 4).

		DISEASE +	DISEASE -
TEST	+	a	b
	-	c	d

Se = a / (a + c)
Sp = d / (b + d)
PPV = a / (a + b)
NPV = d / (c + d)
LR+ = Se / (1 – Sp)
LR- = (1 – Se) / Sp

Univariate testing for comparison of proportions was performed using chi-square test; Fisher's exact test was employed when any of the expected cell numbers in the 2 x 2 tables were less than 5. Measures of association between risk factors and outcome events were expressed as odds ratios (OR). The significance of the odds ratios was assessed using the Mantel-Haenszel chi-square test.

Kappa values for chance-corrected agreement were calculated as one of the measures of the correlation between ordinal variables such as vasospasm defined by TCD and by angiography. Weighted kappa values were used to quantify the interobserver agreement for angiographic vasospasm. Two-tailed unpaired Student's t test was employed as the parametric test of significance for comparison between the means of 2 groups with unpaired continuous data whereas paired t test was used to test for statistical significance of the difference in TCD values during HT and during no HT in the same individuals. The one-way analysis of variance (ANOVA) test provided a comparison of the means of TCD velocities between the 4 categories of angiographic vasospasm: none, mild, moderate and severe. Level of significance was set at $p < 0.05$ and all tests were 2-tailed.

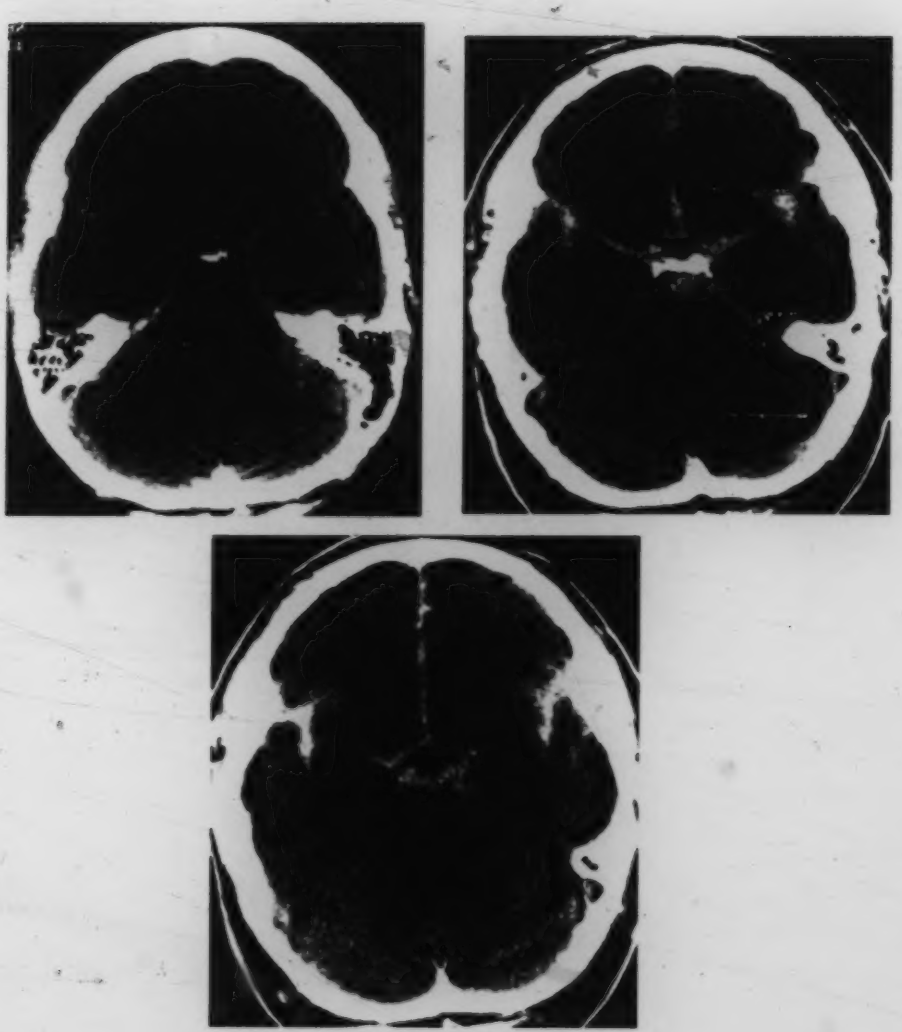


Figure 7: Examples of **thin** subarachnoid blood clot on axial cuts of the initial CT scans of brain.

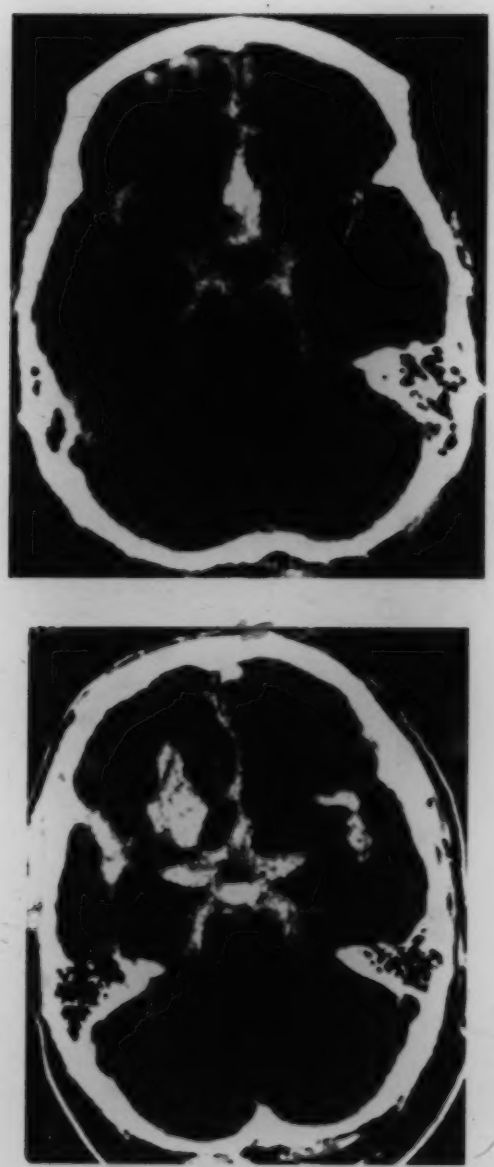


Figure 8: Examples of thick subarachnoid blood clot in the interhemispheric fissure (top) and the basal cisterns (bottom).

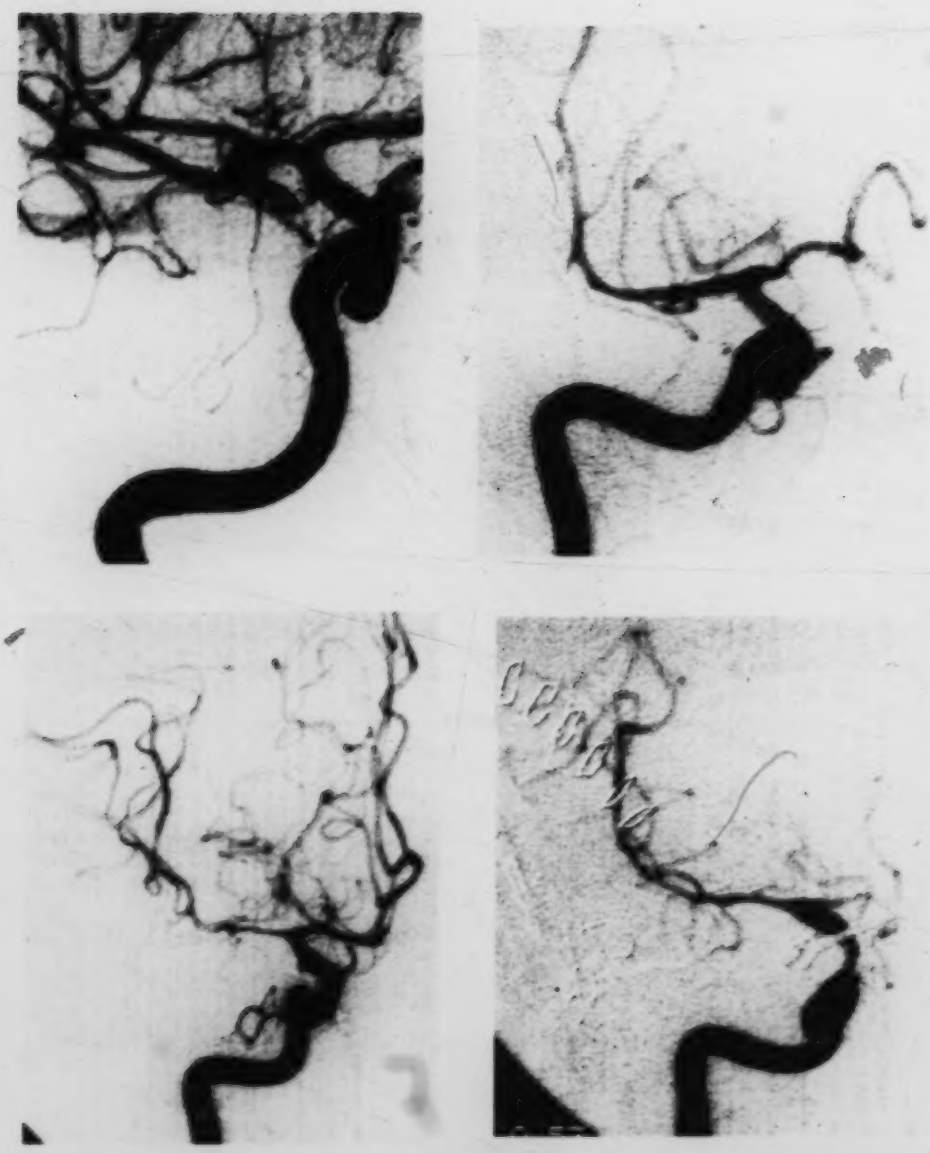
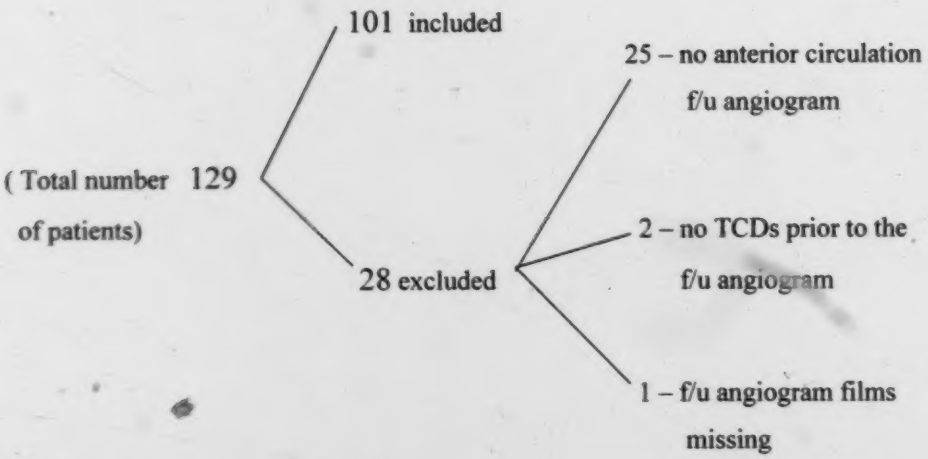


Figure 9: Examples of the various grades of vasospasm on digital subtraction angiography of the right MCA. Starting from the top left and moving clockwise, none, mild, moderate and severe vasospasm are shown.

CHAPTER 3: RESULTS (PART I)

I) DEMOGRAPHICS


101 included
25 – no anterior circulation f/u angiogram
(Total number of patients) 129
2 – no TCDs prior to the f/u angiogram
28 excluded
1 – f/u angiogram films missing

63% of the patients were female and 37% male. The mean age at the time of presentation was 50.5 years, with the range being 17 - 78 years. The mean initial WFNS grade at the time of presentation was 2.3. The grade distribution is shown in

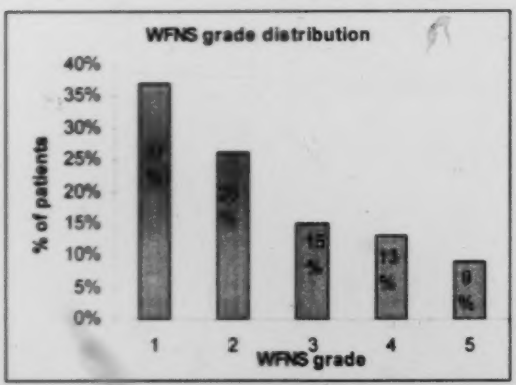


Figure 10: Clinical Grade (WFNS) Distribution on admission

figure 10. The average day of admission was 0.9 days, 85% of the patients being admitted within 1 day and 90% with 3 days. The range was 0 to more than 10 days. Definitive aneurysm treatment (consisting of clipping or coiling) was undertaken at a mean of 1.5 days; 76% of the patients were treated within 1 day and 90% within 3 days. The distribution of the location of the ruptured aneurysm in the 101 patients included in the study was as follows: 37.6% A1-A2 junction, 24.8 % ICA – Pcomm junction, 22.8% M1-M2 junction, 4% basilar tip and 3% ICA bifurcation and 7.8% at other locations (ophthalmic, anterior choroidal, distal anterior cerebral, PICA, SCA, distal P1-P2 junction, vertebral dissecting aneurysm). This is graphically depicted in **figure 11** below:

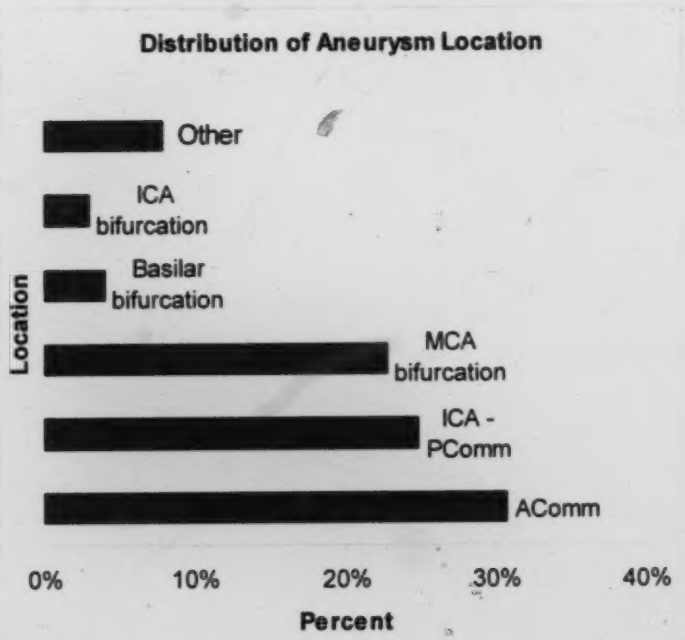


Figure 11: Percentage of total ruptured aneurysms by location

II) TCD – ANGIOGRAPHIC VASOSPASM CORRELATION

Frequencies:

The mean number of TCD exams performed per patient was 8.1. One TCD exam was conducted every 1.2 days on average. 91% (92/101) of the patients had a TCD examination within 1 day of the follow-up (f/u) angiogram. The TCD – angiograhic vasospasm (AV) correlation is based on these TCD values. All patients had a Doppler examination prior to the angiogram. 8 / 202 sides (4.4%) could not be insonated for technical reasons. The mean f/u angiogram day post-SAH was day 8.3, 69% of the angiograms were performed between days 7-10, 88% between days 6-14 and 82% on day 7 or later. The distribution of significant AV by angiogram day is shown in the table below:

F/U angiogram day post-SAH	No. of patients with none/mild vasospasm anywhere	No. of patients with mod/severe spasm anywhere
4-6	6	7 (54%) *
7-10	33	36 (52%)
11-13	6	4 (40%)
≥ 14	1	1 (50%)

Table 1: Prevalence of significant angiographic vasospasm during various time intervals following SAH.

* 12/18 patients had angiograms between days 4-6 had significant vasospasm but to account for selection bias i.e. early angiography in those with DIND (3 patients) or high velocities >160 (2 patients), 5 out of the 12 patients were subtracted, yielding 7/13 patients with significant vasospasm between days 4-6. There was no obvious reason for performing angiography in these 13 patients apart from routine f/u purposes. Hence there was probably

no systematic bias in selecting these patients and therefore these patients probably represented a *random* sample. Even then the incidence of vasospasm was no less during days 4-6 compared with days 7-10 which is the generally accepted period of peak incidence for vasospasm.

A total of 597 vessels (3 × 199 sides) were assessed for angiographic vasospasm in part I of the study. Follow-up angiograms for 3/ 202 sides (2 x 101 patients) = 1.5% were not available. The interobserver agreement (weighted kappa value) for angiographic vasospasm was good: MCA – 0.86, ACA – 0.80, SC-ICA – 0.78 where $k > 0.70$ denotes good agreement. Analysis of the distribution of proximal angiographic vasospasm by location revealed the following:

i) 73% of patients had some degree of AV in one or more vessels. 54% had at least one vessel with moderate or severe spasm.

ii) 60% of the 199 sides had some degree of AV in one of the three vessels evaluated per side (MCA, ACA, SC-ICA). 37% had moderate or severe vasospasm and 17% had severe vasospasm.

iii) 48% of the sides had some degree of AV in MCA, 27% had moderate or severe AV and 12% had severe AV.

iv) Of all sides with moderate or severe vasospasm in any one of the 3 vessels, 73% had it in MCA (i.e. the sensitivity of MCA was 73%). Only 14% of those without moderate or severe MCA vasospasm had it in ACA or SC-ICA (i.e. the negative predictive value of MCA was 86%). In only 4.5% of sides was there severe ACA or SC-ICA vasospasm without the same in the MCA. Of all the patients with DIND from anterior circulation vasospasm, only 13% had significant vasospasm in ACA or

SC-ICA without MCA involvement also. Kappa value of agreement between MCA and significant spasm in any of the vessels was 0.77.

Inferential Data:

A. Results for highest pre-angiogram TCD velocities

The mean pre-angiogram TCD for the two AV groups (considering none/mild vasospasm as "insignificant" vs. moderate / severe or "significant" vasospasm) was 117 vs 164 cm/s respectively ($p < 0.001$). Data for the highest **pre-angiogram** velocity compared with AV in **ipsilateral MCA** considering **mod / severe** vasospasm as "significant" is presented below in **table 2**. Total number of sides available was 186. $P \leq 0.001$ for all categories. The abbreviations used in the table are explained below the table.

TCD velocity (cm/s)	*Se*	*Sp*	*LR+*	*LR-*	*PPV*	*NPV*	*Kappa*
≥120 (n = 112)	0.92	0.51	1.86	**0.16**	0.39	**0.95**	0.30
> 160 (n = 36)	0.46	0.90	4.53	0.60	0.61	0.83	0.39
120-200 (n = 102)	0.77	0.53	1.64	0.43	0.36	0.87	-0.24
≥ 200 (n = 10)	0.23	0.97	**7.91**	0.790	**0.73**	0.78	0.17

Table 2: Predictive value of the highest *pre-angiogram velocity* for significant MCA Vasospasm

Se = sensitivity, Sp = specificity, LR+ and LR- represent likelihood ratios for positive and negative test results respectively, PPV and NPV represent the positive and negative predictive values respectively.

B. Results for TCD velocities obtained within 1 day of the angiogram

The mean velocities for sides with none vs. mild vs. moderate vs. severe MCA vasospasm revealed statistically significant differences (97 vs. 118 vs. 145 vs. 180 cm/s), each group being different from the other three. The mean velocity for significant vs. insignificant AV in the MCA was 162 vs. 103 cm/s ($p < 0.001$). Data for TCD velocities obtained **within 1 day of the f/u angioram** (on the same day in the vast majority of patients) compared with **moderate / severe** AV in **ipsilateral MCA** is presented below in **table 3** (based on 169 values).

TCD velocity (cm/s)	*Se*	*Sp*	*LR+*	*LR-*	*PPV*	*NPV*	*Kappa*	*p*
≥120 (n = 76)	0.88	0.72	3.14	**0.17**	0.55	**0.94**	0.51	0.00
120-159 (n = 43)	0.40	0.80	2	0.75	0.44	0.77	.20	0.01
160-199 (n = 18)	0.31	0.93	3.98	0.85	0.56	0.75	0.26	0.00
≥ 200 (n = 15)	0.27	0.98	**16.39**	0.74	**0.87**	0.77	0.22	0.00

Table 3: Predictive value of TCD velocities for *significant* AV in the ipsilateral MCA

Data comparing TCD velocities obtained **within 1 day of the angiogram** and **moderate / severe** AV in **any of the 3 ipsilateral vessels** is presented below in **table 4** (based on 169 values). $P < 0.001$ for all categories. The abbreviations are the same as above. The number (n) in each velocity category is the same as in Table 3.

Data for TCD velocities obtained **within 1 day of the angiogram** compared with the occurrence of **severe vasospasm** in a) the **MCA** and b) in **any of the three vessels ipsilaterally** is presented below in table 6a and 6b. All the abbreviations are the same as above. The number (n) in each velocity category is the same as in Table 3.

TCD velocity (cm/s)	*Se*	*Sp*	*LR+*	*LR-*	*PPV*	*NPV*	*Kappa*	*p*
≥120	0.91	0.62	2.42	0.14	0.28	0.98	0.27	0.00
120-159	0.26	0.75	1.93	0.85	0.14	0.87	0.01	0.94
160-199	0.22	0.91	2.44	0.86	0.28	0.88	0.30	0.4
≥ 200	0.43	0.97	**12.70**	**0.59**	**0.67**	**0.92**	0.31	0.00

Table 6a: Predictive value of TCD velocites for *severe* ipsilateral *MCA* vasospasm.

TCD velocity (cm/s)	*Se*	*Sp*	*LR+*	*LR-*	*PPV*	*NPV*	*Kappa*	*p*
≥120	0.90	0.65	2.55	0.15	0.36	0.97	0.34	0.00
120-159	0.30	0.76	1.23	0.93	0.21	0.83	0.05	0.53
160-199	0.20	0.91	2.32	0.88	0.48	0.84	0.31	0.4
≥ 200	0.40	0.98	**18.53**	**0.61**	**0.80**	**0.88**	0.29	0.00

Table 6b: Predictive value of TCD velocities for *severe* AV in *any of the three ipsilateral vessels* (MCA, ACA, SC-ICA).

C. Pre-angiogram velocities vs. those within 1 day of the angiogram

Figure 12 below (a receiver-operator characteristics or ROC curves) illustrates the different TCD velocity sensitivity and specificity characteristics (for velocity thresholds of 120, 160 and 200 cm/s) of the highest values obtained pre-angiogram (curve C) and those obtained within 1 day of the angiogram (curves A and B). The latter should correlate best with the angiographic findings. For velocities within 1 day of the angiogram, sensitivity and specificity values for both, spasm in the ipsilateral MCA only (curve A), and spasm in any of the three ipsilateral vessels, MCA, ACA, SC-ICA, (curve B) are also shown below in **figure 12**. These ROC curves are further explained in sections I. 2) b) and I. 3) a) of "Discussion" in chapter 4.

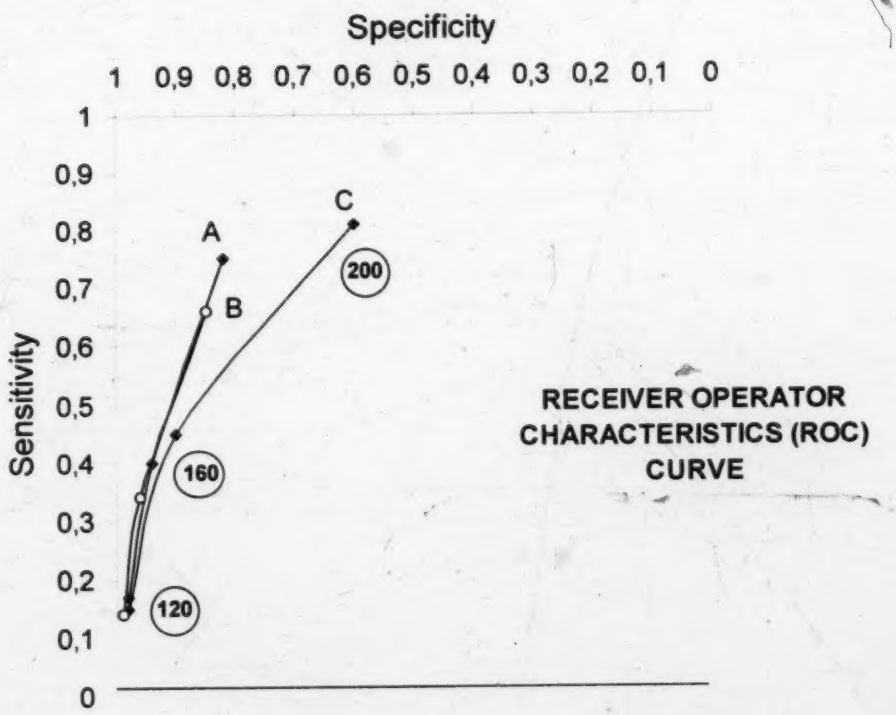


Figure12: Receiver Operator Characteristics curves A, B, C which denote the following:

A- TCD within 1 day of angiogram – MCA vasospasm correlation.
B- TCD within 1 day of angiogram – any of 3 vessels vasospasm correlation (*open circles*).
C- Pre-angiogram TCD – MCA vasospasm.

D. Other TCD parameters

Various other TCD measurements have been studied for their usefulness for predicting vasospasm. They have been listed and referenced in section VI. D) iii) of

"Introduction" in chapter 1. The impetus for examining these parameters was that sometimes it is the trend in the velocities or a comparison with the contralateral side that may have less severe or no vasospasm that are more informative than a single absolute value itself.

Supplementary TCD parameters such as maximum 1 day rise, number of consecutive days of rise, right-left (R/L) difference, maximum - minimum difference in same MCA segment on the same side or in any two segments on either side were also evaluated in this study. They did not improve the predictive value or the sensitivity and specificity of the absolute velocities alone, even when applied in conjunction with absolute velocities. This was due to a large spread for each of the groups and therefore considerable overlap between the insignificant and significant MCA vasospasm groups despite significant Student's t-test results for the difference in their means. The means, p values and the standard deviations for the various TCD parameters are shown below in **Table 7**.

TCD velocity parameter	Mean value / Std. Dev. (*insignificant vasospasm* group) in cm/s	Mean value / Std. Dev. (*significant vasospasm* group) in cm/s	P value
Highest 1 day rise in velocity prior to angiogram	28.7 /20.3	45.6 / 25.5	0.00
Highest consecutive number of days of velocity rise prior to angiogram	1.4 / 0.9	1.7 / 0.9	0.03
Largest velocity difference between any 2 MCA segments prior to angiogram	55.1 / 28.5	94.3 / 40.8	0.00
Largest right-left velocity difference between corresponding MCA segments within 1 day of angiogram	27.5 / 22.4	56.2 / 35.7	0.00
Largest velocity difference in the same MCA segment prior to angiogram	48.9 / 38.1	76.5 / 41.8	0.00

Table 7: Differences in the means of various TCD velocity parameters other than absolute velocities.

Considering the group of patients with absolute velocities between 160 – 199 cm/s within 1 day of the angiogram, 4/5 pts (80%) with R/L difference of > 40 cm/s between corresponding MCA segments developed significant MCA vasospasm on one of the 2 sides, but 2/4 (50%) of those with < 40 cm/s developed such vasospasm. All 5 patients (100%) with a right / left difference of > 40 cm/s developed significant vasospasm in one of the 6 vessels evaluated (3 vessels on each side in the anterior circulation), compared with 2/4 patients with < 40 cm/s right-left difference.

III) INFLUENCE OF SAH CLOT THICKNESS ON AV AND DIND

*1. Relationship with **moderate / severe** vasospasm*

86% of the patients were eligible to have the CT scans of their brain assessed based on presentation within 2 days post-SAH. 25% had "thick" clot in the basal cisterns only, 12% had thick clot in one of the two Sylvian cisterns or the interhemispheric fissure and 1% demonstrated thick clot in both groups of cisterns. The rest of the 62% of patients had only thin clots. Clot thickness was not statistically associated with *moderate / severe* proximal or distal vessel vasospasm considering the six vessels assessed in each patient, collectively. This may have been a reflection of inadequate numbers (as explained below), implying an association albeit a weaker one than the association with *severe* vasospasm.

59% of those without thick clot developed **significant** vasospasm in **proximal or distal** vessels vs. 79% of those with thick clot in either basal or Sylvian / interhemispheric cisterns (OR = 2.6, p = 0.06, 95% C.I. 1.0, 7.1). Hence only a trend toward statistical significance was found possibly because of inadequate patients; when all the numbers in each cell of the 2 x 2 table were multiplied by 2.5, preserving the same proportions as before, the result was significant at p = 0.03. LR+ and LR- for **significant proximal** vasospasm in any of the anterior circulation vessels given thick clot anywhere, were 1.42 / 0.81 respectively. They were also calculated for significant proximal MCA vasospasm given thick clot in basal cisterns or ipsilateral Sylvian cistern. They were 1.72 / 0.73 respectively. This information was used to calculate the cumulative post-test probabilities of significant vasospasm based on the

absolute TCD velocity and clot thickness on admission. The results are shown in the flow diagrams below (**Figures 13a and b**).

Of those with thick clot in one of the Sylvian or the interhemispheric fissures, 82% developed significant vasospasm in a proximal or distal vessel and the location of the vasospasm always matched the clot location, i.e. with a Sylvian clot, the vasospasm involved the ipsilateral MCA and with an interhemispheric clot, the vasospasm involved the ACA. A similar proportion (77%) of those with thick clot in the basal cisterns only, developed significant vasospasm in proximal or distal vessels. This difference was not statistically significant ($p = 0.77$). However the distribution of the vasospasm was different between the two groups. With thick clot in the former distribution, 36% of the patients developed moderate / severe vasospasm in distal vessels vs. 14% with thick clot in the latter distribution (OR = 3.6, $p = 0.06$, 95% C.I. 0.7, 19.4). Again only a trend toward statistical significance was found for this difference possibly because of the small numbers; when all the numbers in each cell of a 2 x 2 table were multiplied by 4, preserving the same proportions, the result was significant at $p = 0.01$.

2. *Relationship with **severe** vasospasm*

Clot thickness was associated with **severe proximal or distal** vasospasm. 55% of patients with thick basal or Sylvian / interhemispheric cistern clot developed severe proximal or distal anterior circulation vasospasm, compared with 15% of those with thin clot who developed such spasm (OR = 8.9, $p < 0.001$, 95% C.I. 3.0, 26.8). It was also associated with severe proximal only vasospasm (OR 9.1, $p < 0.001$, 95%

C.I. 3.4, 24.5). LR+ and LR- for **severe proximal** vasospasm in any of the anterior circulation vessels given thick clot anywhere, were 1.42 and 0.81 respectively. They were also calculated for significant proximal MCA vasospasm given thick clot in basal cisterns or ipsilateral Sylvian cistern They were 2.22 / 0.48 respectively. This information was used to calculate the cumulative post-test probabilities of severe vasospasm based on the absolute TCD velocity and clot thickness on admission. This is shown in the flow diagrams below (**Figures 14a and b**).

3. Influence of clot thickness on the probability of vasospasm

The central portion of the flow diagrams below (**Figures 13 and 14**) shows the probability of the absence or presence of significant or severe vasospasm, depending on the velocity range. The 2 arms on the right show the modified probability if the clot thickness on admission is known. **Figure 13a** below illustrates that with a TCD velocity of < 120, significant ipsilateral proximal MCA angiographic vasospasm will be absent in 94% of cases. It will be absent in proximal MCA, ACA and SC-ICA in 85% of the times. Information regarding the clot thickness does not alter the probabilities very much as the likelihood ratios that can be applied to proximal MCA and any of the three vessel vasospasm are 0.73 and 0.81 respectively. Hence they are both close to 1 and therefore this strategy does not add significantly to the information already available from the TCD velocities without consideration of the clot thickness. The outlined arm illustrates the maximal predictive value possible with a velocity of < 120 cm/s.

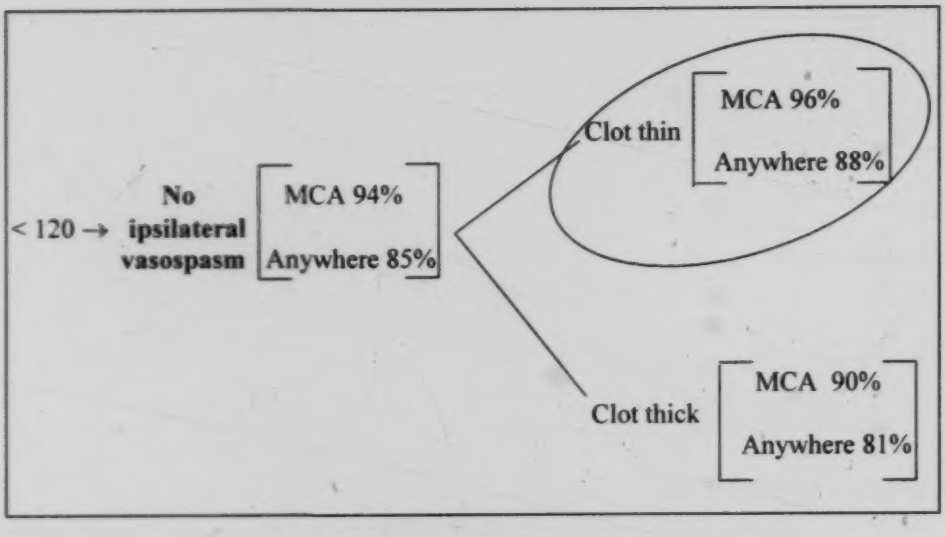


Figure 13a: Probability of no significant proximal ipsilateral vasospasm given a velocity of < 120 cm/s, with thin and thick SAH clots.

- *Only 43% of patients had their highest velocity in the < 120 or ≥ 200 range.*
- *32% of patients fell in one of the 2 outlined arms in figures 13a and b.*

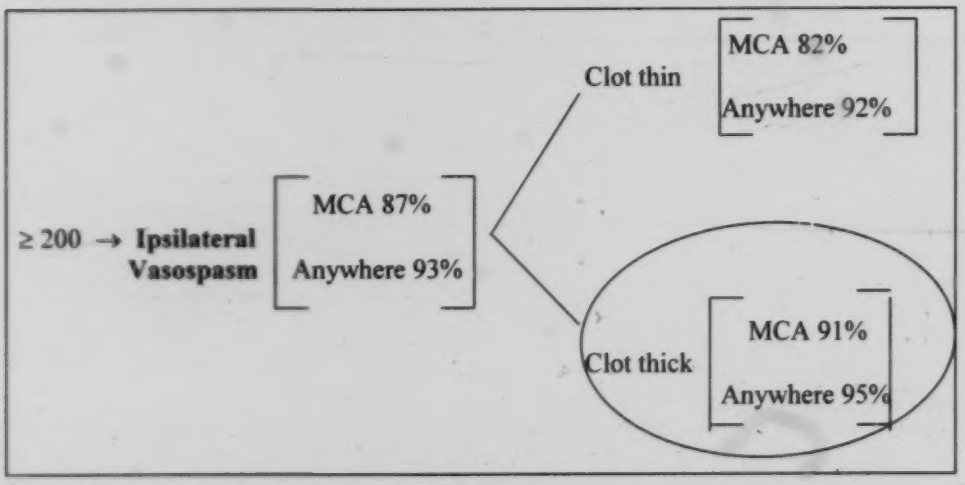


Figure 13b: Probabilities of the presence of significant proximal ipsilateral vasospasm given a velocity of ≥ 200 cm/s, with thin and thick SAH clots.

Figure 13b above shows the probability of moderate or severe proximal vasospasm in the ipsilateral MCA or in any of the three vessels regardless of clot thickness (in the center of the diagram) or given the thickness of the clot (the two arms on the right of the diagram). Again the outlined arm highlights the ideal situation where the velocity is ≥ 200 cm/s and the initial clot was thick.

Figures 14a and b below can be interpreted in the same manner as **Figures 13a and b**, except they illustrate the probabilities for the presence or absence of *severe* instead of moderate / severe ipsilateral proximal vasospasm. For this purpose, as is evident from **Tables 6a and b** above, only a single threshold of 200 cm/s proved to be useful. In this case the impact of clot thickness on the probabilities is higher and it contributes substantially especially for predicting the presence of severe vasospsam if the velocity is ≥ 200 cm/s (**Figure 14b**). "Anywhere" again refers to any of the three vessels one each side, namely the MCA, ACA and the SC-ICA. The outlined arms highlight the ideal scenarios.

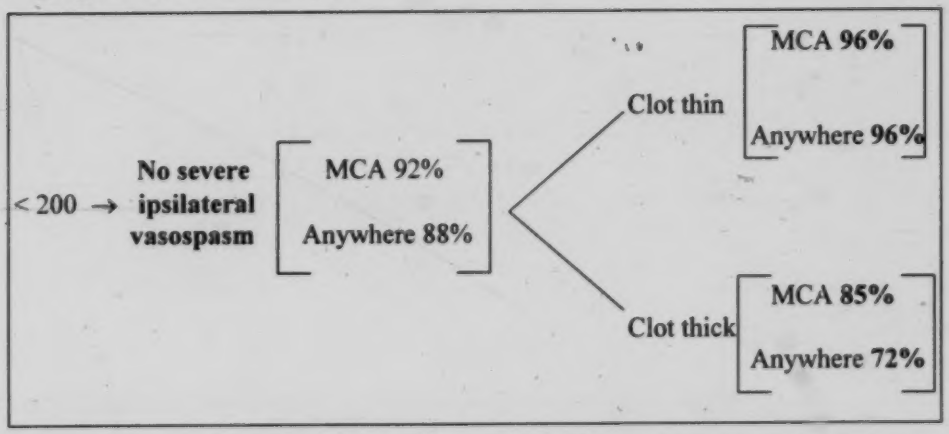


Figure 14a: Probabilities of the lack of severe proximal ipsilateral angiographic vasospasm in the MCA and in any of the three vessels, given a velocity of < 200 cm/s, with thin and thick SAH clots.

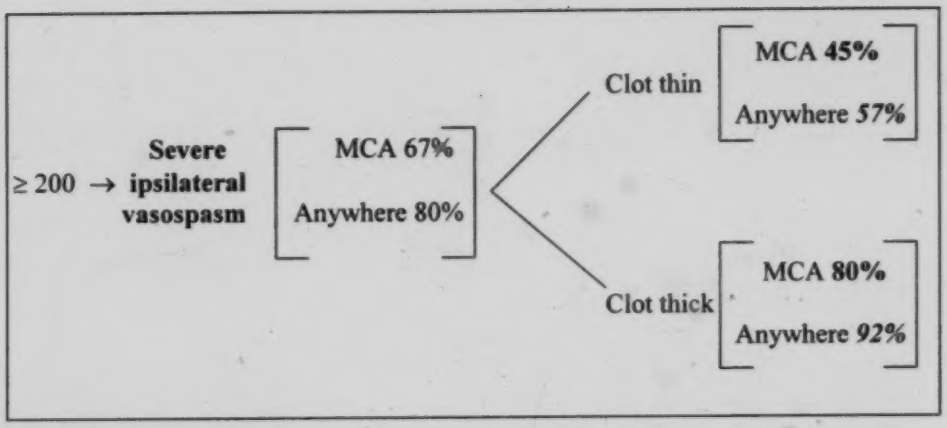


Figure 14b: Probabilities of severe ipsilateral angiographic vasospasm in the MCA and in any of the three vessels, given a velocity of ≥ 200 cm/s, with thin and thick clots.

4. *Relationship of clot thickness with DIND*

There was no association between the location of clot thickness in the basal, Sylvian or interhemispheric cisterns and the occurrence of DIND (OR 1.2, p = 0.6).

IV) TCD – DIND CORRELATION

18% of the patients experienced DIND. However the diagnosis was uncertain in an additional 4% of patients. Of these, one patient had mild angiographic vasospsm, one had moderate and two had severe vasospasm. Hence as many as 20% (including the 3 patients with a possible diagnosis of DIND and with moderate / severe vasospasm) of the patients may have experienced DIND.

The mean highest pre-DIND TCD in those with DIND c/w highest overall TCD in those without, was significantly higher: 179 vs. 144 cm/s, p = 0.003. The distribution of patients based on the maximum TCD velocity prior to DIND as well as the predictive value of TCD at different velocity thresholds are shown below in **Tables 8a and b** respectively. No patient with a maximum velocity < 120 cm/s experienced DIND.

Max. TCD pre- DIND (cm/s)	No. of patients
<120	0
120-159	5
160-199	4
≥ 200	5
Unavailable	3

Table 8a: Number of patients with DIND in various velocity categories

TCD velocity (cm/s)	Se	Sp	PPV	NPV	P value
≥ 120 (n = 57)	1.00	0.25	0.19	1.00	0.20
> 160 (n = 23)	0.57	0.68	0.13	0.95	0.08
> 200 (n = 8)	0.29	0.95	0.33	0.95	0.009

Table 8b: The Predictive Value of TCD for DIND.

V) ANGIOGRAPHIC VASOSPASM – DIND CORRELATION

Moderate or severe proximal angiographic vasospasm was significantly correlated with the occurrence of DIND, OR = 8.72, p = 0.002, 95% C.I. 2.3, 32.8. The distribution of patients with DIND based on the degree of proximal vasospasm is shown below in **Table 9**. There was one patient with moderate and one with severe vertebrobasilar circulation vasospasm and DIND referable to that location, without any significant spasm involving the anterior circulation. The remainder of the 15 patients demonstrated anterior circulation vasospasm and DIND.

Angiographic vasospasm in DIND patient	No. of patients
Severe	10 + 1(vert./basilar) / 17
Moderate	5 + 1 (vert./basilar) / 17
None or mild	0

Table 9: Distribution of vasospasm grade in patients with DIND.

28% of patients with significant vasospasm in the anterior circulation developed DIND. 23% of patients with moderate vasospasm and 33% of patients with severe vasospasm. developed DIND. However given that a significant proportion of patients were receiving prophylactic HT (see section VI. below) without any evidence of DIND, the above low numbers may be low due to "preemptive" treatment in many patients. Only 13% of the patients with DIND due to significant anterior circulation vasospasm did not have involvement of the MCA.

Only 4% of patients with none or mild *anterior circulation* vasospasm. developed DIND – both patients had vertebrobasilar (VB) aneurysms and significant vasospasm in the same distribution. 1 of them had a posterior inferior cerebellar artery aneurysm and the other patient had a basilar tip aneurysm. Hence the NPV of anterior circulation angiograms was 96% overall and 100% in those with anterior circulation aneurysms. LR+ was only 1.91 but LR- was 0.22. Using these likelihood ratios and assuming a pretest probability of DIND of 0.30 (the average literature value), if there is no significant vasospasm on anterior circulation angiograms then the post-test probability of DIND is only 9% overall, and 0% if the ruptured aneurysm was in the anterior circulation. Out of the 3 patients who developed DIND after rupturing a VB aneurysm, 2 demonstrated significant vasospasm just in the VB circulation without revealing any on anterior circulation angiography.

Similar to previous studies (21, 58), 7% of the sides and 10% of all the patients were found to have significant distal (beyond the M1 and A1 segments) anterior circulation vasospasm without such proximal involvement. None of them developed DIND.

VI) HYPERDYNAMIC THERAPY USE

Hyperdynamic therapy was administered in 52.5% of the patients. 40% of HT recipients did not have significant vasospasm and hence its use was considered prophylactic in at least this proportion of patients who were treated with HT. Albumin

was used in 96% of the HT recipients and inotropes or vasopressors were used in 40%. Albumin was given for an average of 5.8 days and inotropes / vasopressors were administered for an average of 4.7 days.

HT use did not correlate with the presence of significant angiographic vasospasm ($p = 0.70$). Among those who received HT, the highest TCD velocity reached during HT vs. during no HT, in the same patients, was significantly higher: 150 vs. 129 cm/s ($p < 0.001$, paired t-test). The highest TCD in patients who received HT vs. those who did not was also significantly higher: 176 vs. 134 cm/s ($p < 0.001$, unpaired t-test). Realizing the possibility that the presence of vasospasm may have led to the administration of HT in a significant proportion of patients and that higher velocities related to HT use may have in fact been due to the accompanying vasospasm rather than the HT itself, the potential role of HT was also evaluated in those without significant angiographic MCA vasospasm. The mean highest velocity reached during HT was higher (146 cm/s) compared to during no HT (127 cm/s) among HT recipients who did not develop significant MCA vasospasm. A paired t-test revealed a trend toward statistical significance for this difference ($p = 0.06$) when a 2-tailed test was used. However considering that HT would not be expected to cause velocities to be lower than during no HT, if a 1-tailed test is used then the difference was statistically significant ($p = 0.03$). Comparing the maximum velocities achieved by patients without significant MCA vasospasm who received HT vs. those who did not receive HT, the mean was significantly higher in the former group (153 vs. 121 cm/s, $p = 0.002$).

VII) OTHER VARIABLES THAT MAY INFLUENCE VELOCITIES

1. Mean arterial blood pressure (MAP)

91 patients had MAP values available on the day of the TCD velocities that were recorded within one day of the angiogram and used for most of the analyses in this study. The MAP at the time of the TCD was used in most cases. When this was not available then the average of the MAPs at the closest time prior to and following the TCD exam was used. When the time of the TCD exam was not known then the average value of all the MAPs between 0800 and 1600 hours on that day was used since all TCD exams are performed between these times. There was no significant difference in the average MAP of the group with moderate / severe MCA vasospasm and the group with none / mild vasospasm at the time of the TCD exam: 102.1 vs. 100.7 mm Hg respectively, $p = 0.63$.

2. Cerebral perfusion pressure (CPP)

Twenty-seven patients required external ventricular drains and intracranial pressure (ICP) recordings. CPP was calculated as MAP – ICP. Values were chosen for comparing the two groups of patients with moderate / severe and none / mild MCA vasospasm at the time of the TCD exam in a similar manner as for MAP above. There was no significant difference between the groups: 92.3 vs. 96.9 mm Hg respectively, $p = 0.44$.

3. Hematocrit

57 patients had hematocrit values on the day of the TCD exam that was within one day of the follow-up angiogram. If multiple blood counts were performed on that day then the value closest in time to the TCD exam was used, otherwise the single value obtained that day was used. The mean hematocrit in patients with moderate / severe MCA vasospasm and those with none / mild vasospasm was identical at 33%.

4. Central venous pressure (CVP)

20 patients had CVP recordings. Values were chosen as for MAP above. The mean CVP in those with moderate / severe MCA vasospasm was slightly lower than in those with none / mild vasospasm but not significantly different: 8.6 vs. 10.3 mm Hg, $p = 0.41$.

VIII) RISK FACTORS FOR VASOSPASM

The impact of clot thickness on vasospasm was discussed previously in section III. Clinical grade was not associated with significant or severe vasospasm in proximal vessels, when grades 3, 4 and 5 or when grades 4 and 5 were grouped together (p values ranging from 0.13 to 0.52).

The incidence of moderate / severe or just severe vasospasm, proximally, or proximally and distally, was not associated with the use of either tissue plasminogen activator (TPA) or papaverine, intraoperatively or postoperatively. This was true

when all patients (a total of 19 patients received TPA) and when only those with thick clot (5/15 patients with thick clot received TPA) were considered, p = 1.00 for both. This may be due to small numbers.

IX) TCD-TIME PLOTS

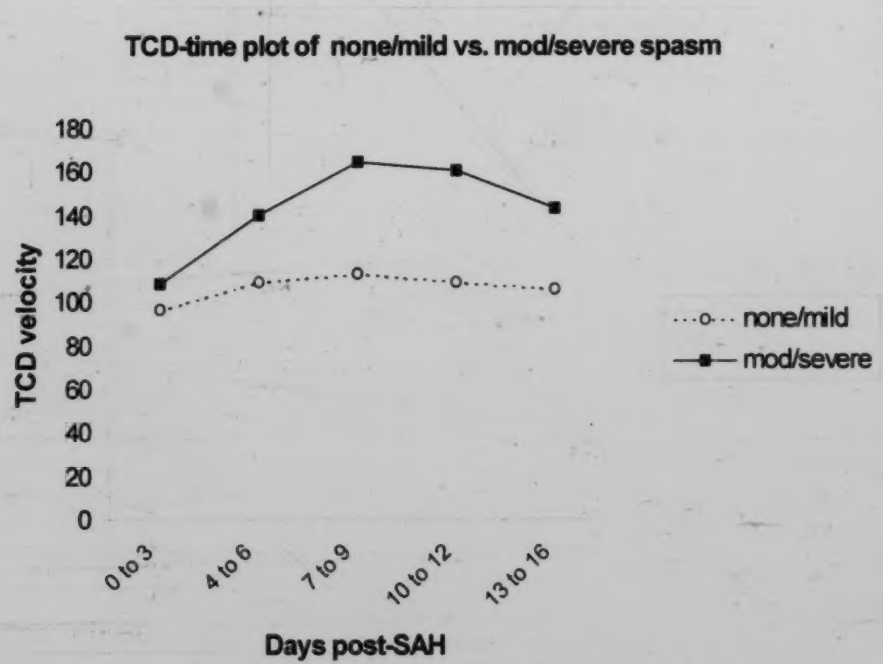


Figure 15: TCD velocity vs. time comparing patients demonstrating none / mild proximal MCA vasospasm angiographically, with those demonstrating moderate severe vasospasm.

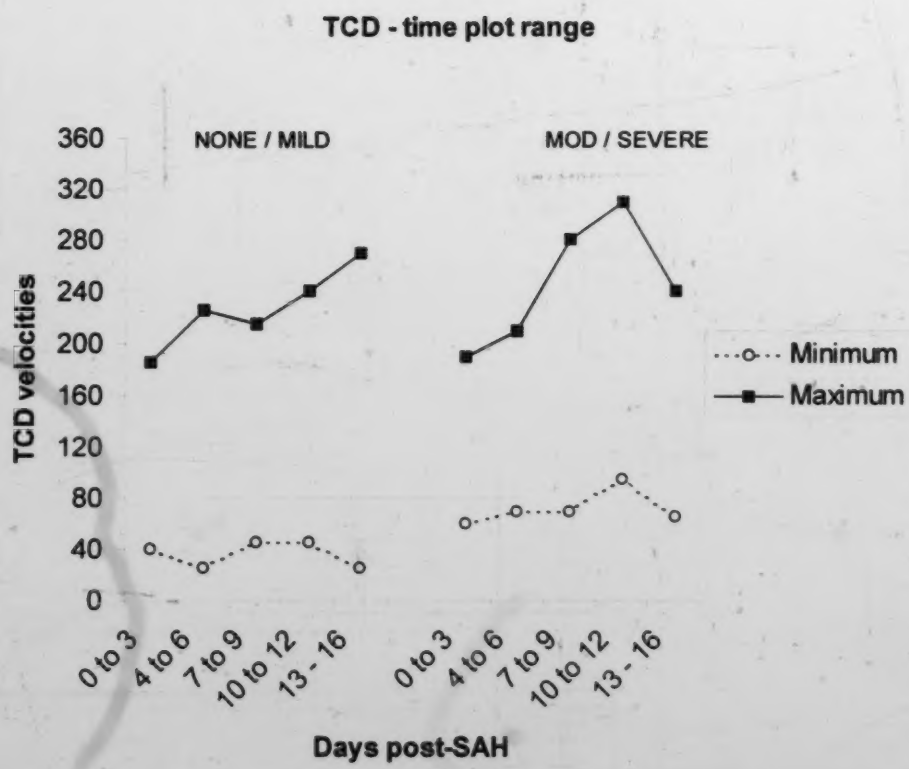


Figure 16: TCD velocity range vs. time comparing patients with none/mild vs. moderate / severe proximal MCA angiographic vasospasm.

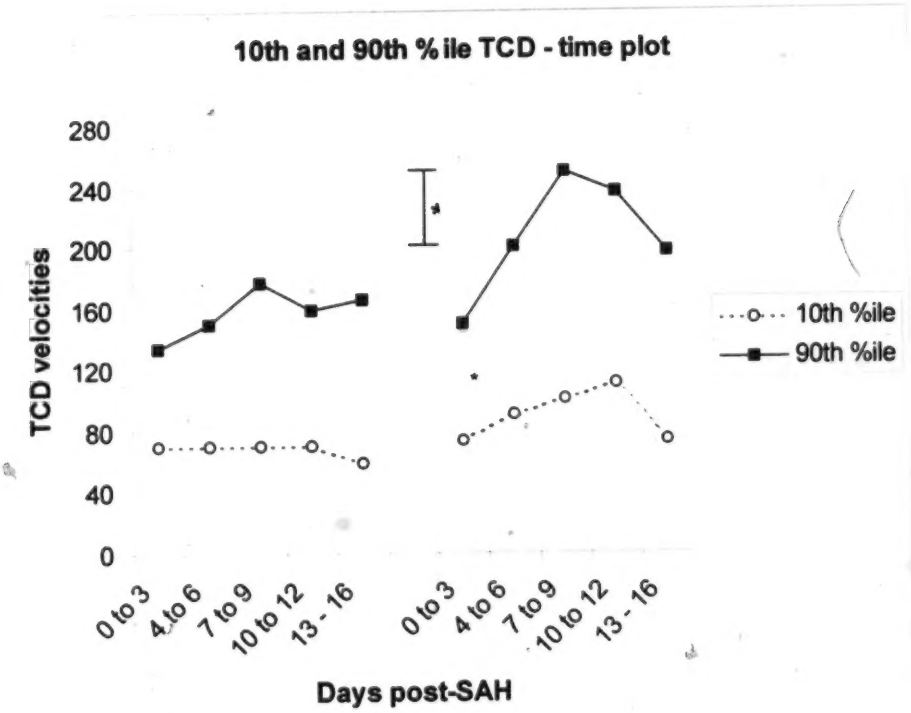


Figure 17: The range between 10th and 90th %ile TCD velocities in patients with none / mild vs. moderate / severe angiographic vasospasm in the proximal MCA.

* Only 43 / 860 values (5%) were 200 cm/s or greater (the zone of difference between the 2 groups above) in the moderate/severe spasm group.

X) INCLUDED VS. EXCLUDED PATIENTS

Figure 18 below reviews the rationale for excluding the 28 patients in part I of the study.

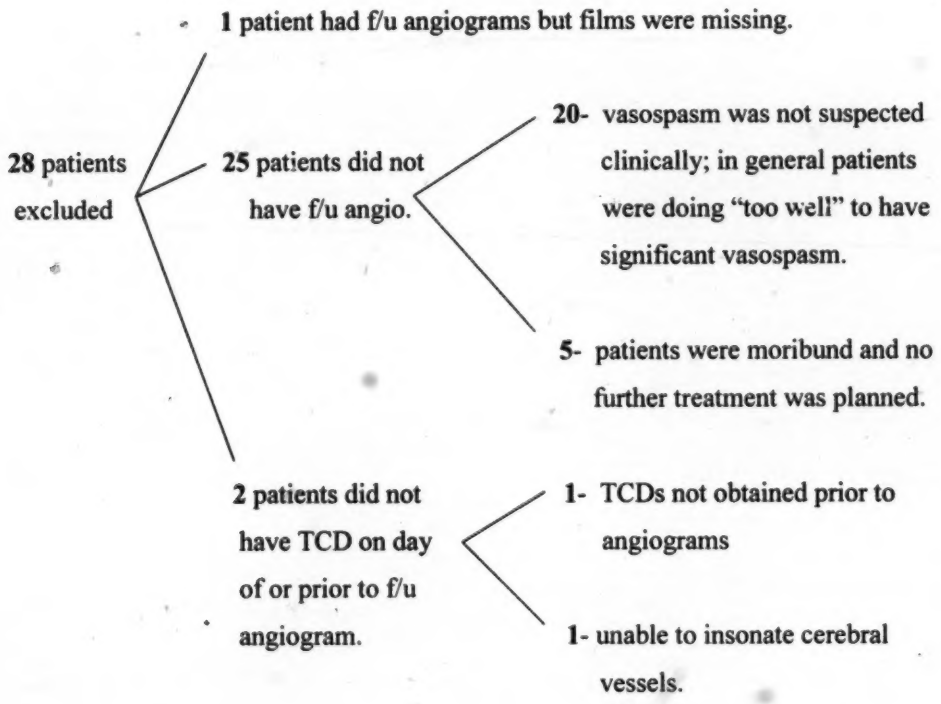

1 patient had f/u angiograms but films were missing.
28 patients excluded
25 patients did not have f/u angio.
20- vasospasm was not suspected clinically; in general patients were doing "too well" to have significant vasospasm.
5- patients were moribund and no further treatment was planned.
2 patients did not have TCD on day of or prior to f/u angiogram.
1- TCDs not obtained prior to angiograms
1- unable to insonate cerebral vessels.

Figure 18: Reasons for the exclusion of patients in part I of study.

Table 10 below compares various patient characteristics between the included and excluded group. The p values for any difference between the two groups is also shown.

Patient Characteristic	Included (n = 101)	Excluded (n = 28)	p
Age	56.1	50.1	0.10
% females	63.4	82.1	0.07
WFNS grade	2.32	2.33	0.98
Admission day	0.90	2.07 (1.65) *	0.06
Day of definitive Rx.	1.46	4.50 (2.65) **	0.06
No. with thin : thick clot	63 : 23	16 : 3	0.90
% receiving HT	52.5	35.7	0.12
% receiving albumin	50.5	35.7	0.17
Albumin: no. of days	5.8	3.8	< 0.001
% getting inotropes/pressors	20.8	0	0.007
Inotropes/pressors: no. days	4.7	0	< 0.001
% developing DIND	18	0 ***	0.20
No. TCD exams performed	8.1	5.9	0.001
Highest velocity (mean)	141 cm/s	110 cm/s	< 0.001

Table 10: Comparison of patient characteristics between the included and excluded patients.

* One patient was admitted on day 13 and therefore the mean was skewed to the right given the small n value. After excluding this patient the mean value in brackets was obtained. The p value represents the significance of the difference prior to making this adjustment, i.e. for 0.90 vs. 2.07.

** Two patients demonstrated extreme values: the above patient admitted on day 13 was clipped on day 16 and another patient admitted on day 0 subsequently deteriorated and was therefore not clipped until day 36. The value in brackets represents the mean after excluding these two outliers. However the p value again was calculated to reflect the significance of the difference without this adjustment, i.e. for 1.46 vs. 4.50.

*** None of the excluded patients developed DIND; one patient was admitted with an infarct secondary to severe vasospasm already in progress. This difference was not statistically significant due to the relative infrequency of DIND in the included group and the relatively small number of patients in the excluded group.

PART II - RESULTS

I) Demographics

Figure 19 below compares the number of included and excluded patients in part II of the study.

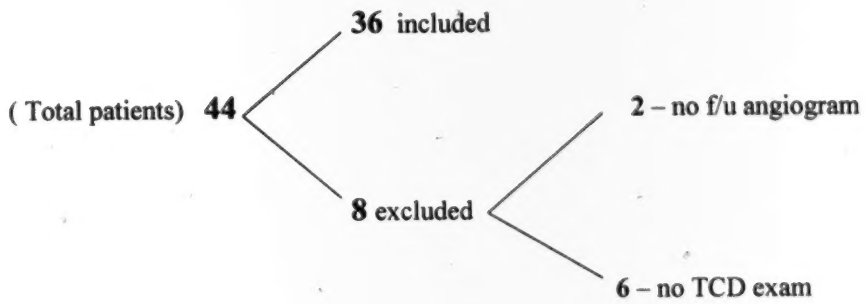


Figure 19: Included versus excluded patients in part II of the study.

The average age of patients in part II of the study was 54.6 years. 22.2% were males and 77.8% were females. The mean admission day post-SAH was 1.56 but

there were 3 extreme values (7, 14 and 21 days). If these three values are excluded then the mean becomes 0.42 days. 89% of patients were admitted within 3 days of SAH. Mean definitive aneurysm treatment day was 2.55 but if the above 3 patients are excluded then the mean becomes 1.45 days. 83% of the patients were treated within 3 days of SAH. The WFNS grade distribution was as follows: grade 1 – 41.7%, grade 2 – 8.3%, grade 3 – 8.3%, grade 4 – 16.7%, grade 5 – 25%.

II) Lindegaard Ratio– Angiographic Vasospasm Correlation

The mean Lindegaard ratio in those with none / mild proximal MCA vasospasm vs. those with moderate / severe vasospasm was 1.74 vs. 2.63 ($p = 0.02$). Univariate analysis using Lindegaard ratio > 3 to define vasospasm revealed significant association ($p = 0.002$). However, Se = 0.45, Sp = 0.94, PPV = 0.63 and NPV = 0.89.

III) Lindegaard Ratio – DIND Correlation

23% of the patients experienced DIND. There was no significant difference in the maximum pre-DIND Lindegaard ratio of those with DIND vs. the maximum ratio in those without DIND: 2.75 vs. 2.28, $p = 0.26$.

IV) INFLUENCE OF HT ON LINDEGAARD RATIO

The Lindegaard ratio was similar during HT vs. during no HT in patients who were administered HT: 2.58 vs. 2.35, ($p = 0.49$).

CHAPTER 4: DISCUSSION

Since its introduction in 1982, transcranial Doppler ultrasonography has gained widespread acceptance as a safe and non-invasive tool to establish the presence of cerebral vasospasm. It is employed at most neurosurgical centers throughout the world to monitor the development of vasospasm following subarachnoid hemorrhage. As mentioned in the introduction, TCD velocities are being used to help plan the timing of surgery, to definitively diagnose vasospasm without confirmation by angiography (the current gold standard) and to guide treatment. In addition, clinical studies involving post-SAH vasospasm as one of the variables being investigated have used TCD velocities to define it (22, 71, 153).

Previous studies have focused on the overall general relationship between TCD velocities and angiographic or clinical vasospasm by calculating the correlation coefficients or comparing sample means using Student's t test. Although useful as evidence of the presence of a relationship and as descriptors of the nature of this relationship, they are of little help to the clinician by the bedside who wishes to estimate the likelihood of clinically significant vasospasm based on the individual's TCD velocities before proceeding with invasive and potentially harmful investigative or treatment measures. For such purposes one desires data regarding the positive and negative predictive values and the likelihood ratio for the diagnostic test. The calculation of these parameters was demonstrated earlier in "Methods" (chapter 2). The positive predictive value of a test denotes the probability of true disease given a positive test whereas the negative predictive value denotes the probability of true

absence of disease given a negative test. Sensitivity and specificity fail to provide a direct indication of these probabilities; the former refers to the probability of a positive test in the true presence of disease whereas the latter refers to the probability of a negative test when the disease is truly absent. *True* presence or absence of disease is measured using the *gold standard* diagnostic test. Likelihood ratios provide yet another measure of the value of test. LR+ is the ratio of the proportion of positive tests among those *with* the disease, to the proportion of positive test among those *without* the disease; hence it is the same as Se / (1 – Sp). LR- is the ratio of the proportion of negative tests among those *with* the disease, to the proportion of negative tests among those *without* the disease; hence it is the same as (1 – Se) / Sp. They are useful for several reasons. They allow for the calculation of post-test probability of disease given the pre-test probability of disease. The latter is often just the prevalence of the disease in the population; in this case the use of LR+ will simply yield the PPV and the use of LR- will simply yield 1 – NPV. However if one can modify the pre-test probability by applying multiple tests serially or by selecting subjects that are at higher risk of developing disease then the probability of the presence or absence of disease can be substantially augmented. Likelihood ratios are most influential when their values are as far away from 1 as possible; ideally the LR+ of a good test should be at least 5 to 10 and the LR- should be less than 0.1 to 0.2. In order to obtain the post-test probability of disease, one must first convert the pre-test probability into odds, then multiply the odds by the likelihood ratio to get the post-test odds and then convert the odds into post-test probability. Hence for example if the baseline or pre-test probability of disease is 25% and a diagnostic test #1 with a

LR+ of 5 is positive then the post-test probability of disease can be calculated as follows:

Pre-test probability 0.25 = pre-test odds 1:3

(Pre-test odds) x (LR+) = post-test odds #1 of 5:3 = post-test probability #1 of 5/8 or 62.5%. Now if a second diagnostic test of LR+ = 4 is also positive then,

Post-test odds #2 = 20:3. Hence the final post-test probability of disease = 20/23 = 87%. One caveat in applying serial tests as above is that the tests must be independent of each other, i.e. the results or performance of one test should not be able to influence the other. Another advantage of likelihood ratios is that they are independent of the prevalence of the disease, unlike the positive and negative predictive values. Hence these ratios are dependent only on the test itself and can therefore be applied under varying clinical circumstances.

Only a few studies have investigated the predictive value of TCD and they considered even slight or mild vasospasm of otherwise little clinical relevance as a positive angiographic result for calculating the predictive value of TCD (51, 54, 92, 118); they did not distinguish between clinically significant and insignificant vasospasm. Other methodological concerns have been outlined previously in the introduction section VI A.

A unique opportunity existed at this institution to obtain the above information because TCD exams are routinely performed on all SAH patients starting day 3 to 4 post-SAH and follow-up cerebral angiograms are also routinely performed on most patients, primarily to confirm adequate exclusion of the treated aneurysm from the circulation. The decision to perform an angiogram is made independent of

the TCD velocities unless there is a strong clinical suspicion of the presence of significant vasospasm and the clinician wishes to confirm or rule out this diagnosis so that appropriate treatment may be administered. However even in this case only the timing of the angiogram is influenced as it is obtained earlier than it might have been otherwise. Angiograms are performed during the vasospasm risk period of days 4 – 21 post-SAH so that the clinician may also be alerted to the presence of any significant cerebral vasospasm. Most of the angiograms are performed during the peak risk period and this is evidenced in this study by the fact that 88% of the patients had the follow-up angiogram between days 6-14 post-SAH which distinguishes this study from previous ones. This study is also unique in being one of the largest series to investigate the questions outlined above and specifically distinguishing between "insignificant" and "significant" vasospasm which is what the clinician is really interested in.

Another noteworthy point of distinction is that 52% of the patients in this series received hyperdynamic therapy, a significant proportion of whom (40% of the HT recipients) did not demonstrate significant vasospasm, reflecting its prophylactic role in these patients. This is consistent with the observation that in this study HT use was not statistically associated with the presence of significant vasospasm ($p = 0.67$). This variable was documented to evaluate its potential impact on TCD velocities. One of the strengths of this study lies in the use of 2 independent and blinded observers who compared all the angiograms with the baseline films using ≥ 2 views to evaluate vasospasm based on pre-defined criteria; this minimizes the measurement bias in such a study. In addition, the number of TCD exams per patient (mean 8.1), on average

every 1.2 days and spanning the critical vasospasm risk period (days 4-14) post-SAH compares favorably with the frequency of TCD exams at other institutions throughout North America (118, 154). It is therefore unlikely that relevant TCD data for the studied patients was omitted. Previous studies correlating TCD velocities with cerebral angiographic vasospasm are summarized in **Table 11** below.

Reference	# of patients in whom TCD and AV correla-ted	# of patients with angios. during vsp. period	Significant angiographic vasospasm seperated from insignificant vasospasm	Independent and blinded observers evaluated angiographic vasospasm ?	PPV NPV LR+ LR- given	Prophlactic HT used ?	Nature of TCD-AV agreement
Aaslid et. al., 1984	24	10	No	No	No	Unknown	r = -0.75
Compton et. al., 1987	20	Unclear	No	Single blinded observer	PPV, NPV.	[illegible]	[illegible] = 0.8, NPV>0.9, no correlation between FV and severity of vsp., wide variation of FV makes statistical interpretatio-n difficult.
Harders et. al., 1987	8	8	No	No	No	Unknown	r = -0.7087
Lindegaar d et. al., 1988	51	5	Yes	No	PPV	Unknown	r = -0.905, PPV= 0.86-0.98, "Specificity differentiatin-g between mild and pronounced MCA spasm was only 0.54".
Sekhar et. al., 1988	21	12	No	No	No	Unknown	r < -0.25, poor correlation.
Hutchison and Weir, 1989	50	27	Yes but no objective criteria.	No – radiologists' reports used to determine	No	Yes	Difference in means of "severe" vs. "mild or no

				vasospasm.			vsp" not statistically significant, wide variation in values in individual and between patients.
Lindegaard et. al., 1989	79	Unclear 8 / 79 patients had follow-up angio.	Yes but vsp. grading not based on change from baseline angiogram.	Two independent observers. ? blinded.	No	Unknown	Fair to moderate agreement (kappa 0.35-0.47) between severe MCA vsp and velocity > 150 cm/s
Grosset et. al., 1993	102	34	No but exact vessel diameters measured.	Single blinded observer	No	Unknown	r = -0.54.
Burch et. al., 1996	49	49	Yes (basis for grading % stenosis unclear)	Blinded but ? single observer	PPV, NPV	Unknown	PPV = 0.73-0.87, NPV = 0.65-0.78, poor (but statistically significant) correlation with vsp. grade
Creissard et. al., 1995	40 Only patients with angiog-raphic vsp. were studied.	40	Yes	No	No	Unknown	"Transcrania -l Doppler remains a mediocre tool for indentifying vasospasm.." Sensitivity = 0.76.
Wardlaw et. al., 1998	82	Not stated	No. Method of assessing angiographic vasospasm not specified.	No	PPV and NPV indir-ectly state-d	Unknown	PPV and NPV=1. "TCD .findings correspond closely to…. angiography ".

Table 11: Summary of previous studies investigating the correlation between absolute TCD velocities and angiographic vasospasm of the MCA

I) TCD – ANGIOGRAPHIC VASOSPASM CORRELATION

1) The validity of the choice of MCA for ultrasonography:

As explained in section IV. B. ii. of the *Introduction*, the MCA has been found to be the most appropriate intracranial vessel for TCD examination to detect vasospasm. Its negative predictive value was 86% for clinically significant vasospasm and 95.5% for severe vasospasm in either the M1, A1 or SC-ICA, indicating that it serves as a valid representative for significant angiographic vasospasm affecting any of the above major vessels of the anterior intracranial circulation. The kappa value of agreement beyond chance between significant spasm in the MCA and in any of the three vessels was 0.77, supporting the above claim. Furthermore only 13% of patients with DIND from anterior circulation spasm failed to demonstrate significant vasospasm of the MCA.

2) Absolute TCD velocities within 1 day of the follow-up angiogram

a) *Comparison with significant (moderate or severe) MCA vasospasm*:

Given the previously mentioned applications of TCD velocities in the management of SAH patients, it would be reasonable to expect a PPV of *at least* 80% prior to undertaking more invasive measures, and a NPV of *at least* 90% before repudiating the need to treat or further investigate vasospasm. Even with the above minimum standards and conservatively estimating the average number of treatable aneurysmal SAH patients at a major neurosurgical center at 1.5 patients (i.e. 3 MCAs)

per week, one would miss significant vasospasm once every 3-4 weeks and over-investigate or unnecessarily treat once every 1-2 weeks. With a NPV of 95% and PPV of 90% one would miss important spasm 7-8 times per year and over-investigate or treat once every 3-4 weeks. These are not unreasonable ideals.

Comparing the TCD values within 1 day of the follow-up angiogram with the angiographic vasospasm **(Table 3)** revealed that only velocities less than 120 cm/s and greater than or equal to 200 cm/s surpass the minimum standards and approach the ideals above. The NPV of velocities < 120 cm/s was 94% and the positive predictive values of velocities ≥ 200 cm/s was 87%. Similarly the likelihood ratios for the two categories are sufficiently extreme at 0.17 and 16.39 respectively so as to be influential if the pre-test probability of vasospasm is known. The pre-test probability was equivalent to the prevalence of vasospasm in this patient population. The likelihood ratios for velocities between 120 and 200 cm/s were close to 1 and therefore of little consequence. Values > 120 cm/s were not discriminating for the absence of consequential vasospasm; the NPVs for all the categories were similar at about 75%. With velocities below 200 cm/s, the PPV for such spasm declined markedly at 44%-56% which is no better than the toss of a coin by the bedside. Note that the kappa values for overall agreement beyond chance between TCD and angiography range from 0.20-0.51, all being sub-optimal for such a test. This is because only a minority of patients fall in each of the only two useful categories of < 120 or ≥ 200 cm/s. Only 43% of patients had maximum velocities in the clinically useful ranges of either < 120 or ≥ 200 cm/s.

Another point to note is the p values in each category in **Table 3** are highly significant at ≤ 0.01 and the mean velocities for those with insignificant vs. significant vasospasm were significantly different. Furthermore the mean velocities in each of the 4 categories of none, mild, moderate and severe MCA vasospasm were also significantly different by the ANOVA test and post-hoc analysis revealed that each group was different from the other three. This underscores the importance of considering not only the presence of a statistically significant association but the nature and magnitude of that association which ultimately reflects the clinical significance. In this case the statistical significance of the results failed to faithfully portray their clinical significance. This important concept is graphically illustrated in **Figures 15 – 17** in section VIII of the results which plot the highest absolute MCA velocities for days 0-3, 4-6, 7-9, 10-12 and 13-16 following SAH. **Figure 15** shows that when only the overall means are considered, there is a significant difference between those with none or mild vs. moderate or severe MCA vasospasm. However what is more important and relevant to the clinical management of individual patients is appreciated from the latter two plots. **Figure 16** demonstrates that when the entire range of values is considered for the two groups then it is difficult to distinguish between the groups and even when the extreme 10% of values are excluded (**Figure 17**), there is still a considerable overlap The zone of difference in **Figure 17** (values ≥ 200 for the moderate / severe vasospasm group) is applicable to only a small proportion of patients as only 5% of the values fell in this range.

b) *Comparison of MCA velocities with significant spasm in any of the 3 vessels:*

The NPV of velocities <120 cm/s for spasm in any of the three vessels ipsilaterally considered together was 85% and the PPV of values ≥ 200 was 93% **(Table 4)**. The lower NPV but higher PPV in comparison to MCA vasospasm is understandable because in some of the patients without significant vasospasm in the MCA, it may still be present in one of the other two vessels. This would decrease the NPV but increase the PPV.

Data was also analyzed considering each patient as a whole instead of by each side separately for the ipsilateral TCD and angiogram results. Thus the highest mean MCA velocity on either side was compared with the angiographic findings in both the MCAs as well as in any of the 6 vessels on either side (the MCA, ACA and SC-ICA on each side). As seen in **Table 5**, the results were similar except that the PPV of velocities between 160-199 cm/s for significant vasospasm in *any of the six vessels* assessed per patient was 82% which is considerably higher than the results by sides. This difference however may be misleading and due to chance because one is bound to find some of the patients without MCA spasm to have spasm in at least one of the other 4 vessels thereby "falsely" driving up the PPV. Similarly the PPV of velocities between 160-199 cm/s for *MCA* spasm on either side (since each patient is considered as a whole), was higher at 73%. Again this may be expected as some of the patients without ipsilateral MCA spasm may have contralateral MCA spasm, hence augmenting the PPV just due to chance. Even at 73% however it falls short of the standards for the PPV and NPV suggested above.

These findings are illustrated in **Figure 12** by comparing the Receiver Operator Characteristic curves (ROC curves)"A" and "B". They show that at a given velocity threshold, the sensitivity for spasm in *any of the three vessels* is lower than in the *MCA alone* because MCA velocities may not reveal angiographic spasm in the ACA or SC-ICA as consistently as just in the MCA. In fact one would expect that with significant spasm in the SC-ICA, the flow and hence the velocities distally in the MCA would be lower due to the increased resistance proximally in the circuit. The specificity at each velocity threshold is however almost identical for both curves. Based on anatomical and physiological principles it is probably most accurate to correlate the TCD velocities in a vessel with the angiographic appearance of the same vessel on the ipsilateral side. Therefore the association between TCD velocities and specifically the *ipsilateral MCA* angiographic findings are likely to be most reliable and reflective of the true relationship.

c) *Special precaution regarding those with velocities in the 160-199 range*:

In the 160-199 cm/s group, a right-left difference of >40 cm/s between corresponding MCA segments indicated the patient was at high risk (80%) for having significant vasospasm in the MCA and especially in one of the three vessels (100%) evaluated in the anterior circulation. This was in contrast to a 50% incidence of vasospasm in those with a right-left difference of < 40 cm/s. However the number of cases is small and hence the above observation should not be treated as a "rule" but rather as a statement of caution.

*d) TCD correlation with **severe** vasospasm in the MCA and in any of the 3 vessels*:

In order to predict the presence or absence of severe (as opposed to moderate/severe) spasm, a single useful cut-off point of 200 cm/s emerged **(Tables 6a & 6b)**. The NPV for the absence of severe MCA vasospasm with velocities below 200 cm/s was 92% but the PPV for values ≥ 200 cm/s was only 67%. This improves substantially if the initial blood clot on CT is thick. Considering spasm involving any of the 3 vessels, the NPV was similar at 88% but the PPV was substantial at 80%. This again reinforces the previous conclusion that 200 cm/s is the lowest useful absolute velocity threshold for predicting significant cerebral vasopspasm with a reasonable degree of certainty. Velocities < 200 cm/s were not useful for diagnosing **severe** vasospasm.

3) **Highest absolute TCD velocity pre-angiogram:**

a) *Predictive value in comparison with velocities within 1 day of angiogram*:

The angiographic findings for the MCA were also compared with the highest mean MCA velocity obtained ipsilaterally anytime prior to and including the day of the angiogram, instead of the velocities within 1 day of the angiogram. **Table 2** shows that the NPVs of velocities in all three categories of less than 120, 160 and 200 cm/s, were very similar to the corresponding values calculated using the velocities within 1 day of the angiogram (within 3%). However the PPV of velocities in all categories was considerably lower, ranging from 36% (for velocities between 120-200 cm/s) to 73% (for velocities ≥ 200) with the differences ranging from 7% to 20%. This is graphically illustrated in the ROC curves "A" vs. "C" (**Figure 12**) which show

that at each of the three velocity thresholds the sensitivity is similar but the specificities are markedly different at velocities above 160 cm/s and therefore the two curves deviate away from each other. The ideal ROC curve would conform along the y-axis on the left and then horizontally along the x-axis at the top, as closely as possible and would include an inflection point at the upper left hand corner of the graph which would correspond to the velocity that has a sensitivity and specificity of 1. Curve A is clearly superior in this respect compared to curve C; this is not surprising as one would expect the velocities obtained closest to the time of the angiogram to be the most representative of the angiographic findings. A diagnostic test that was of little use would be represented by a diagonal line from the bottom left corner to the top right corner of a ROC curve.

b) *The possibility of "early" cerebral vasospasm in some patients*:

If one considers cerebral vasospasm to be a monophasic event such that there is a single continuous rise to its maximum severity followed by a gradual continuous decline then one possible explanation for the observation in section a) above is that there are higher velocities prior to within 1 day of the angiogram and they subside by the time of the angiogram and therefore corrrelate poorly with reduced spasm seen on the angiogram (hence the lower PPV). This may be due to a significant number of patients achieving peak spasm on days 4-6 thereby attaining higher velocities but because > 80% of the angiograms were performed on day 7 or later, the angiogram may be capturing the vasospasm during its decline in these patients and hence the lower velocities within 1 day of the angiogram. Increased use of HT prior to day 7

compared with afterwards was not evident and therefore cannot account for falsely elevated velocities early on. The above possible explanation for the lower specificity and PPV of the highest *pre-angiogram* velocities compared to those *within 1 day* is supported by the finding that the incidence of significant vasospasm among those who underwent angiography (for seemingly routine purposes without any obvious selection bias for the more severely afflicted patients) between days 4-6 was no less than after day 6, specifically between days 7-10 (see **Table 1**). This held true even after 5 of the 12 patients who had angiograms performed for clinical suspicion of vasospasm were excluded to yield a group of patients that appeared to represent an unbiased selection of patients who underwent "early" angiography.

Another observation that is consistent with above is that just as many (7/15) patients with anterior circulation DIND were diagnosed as such on day 6 or before, compared to between days 7-10 (7/15). 1/15 patients demonstrated DIND at the time of admission 1-2 weeks after the SAH and hence the onset of DIND could not be accurately timed. One of the "early DIND" patients experienced right sided hemiparesis on day 3 and an angiogram 2 days later revealed isolated moderate vasospasm affecting the left MCA. These findings raise the possibility that a substantial number of patients may be susceptible to developing significant cerebral vasospasm early in the course rather than between days 7-10 which has traditionally been considered to be the time period for the peak incidence of vasospasm.

There were 2 patients in this study who had follow-up angiograms on days 5 and 6 respectively that demonstrated severe vasospasm and, as mentioned above, 1 patient developed DIND on day 3. His angiogram on day 5 revealed moderate

vasospasm. It follows that although rare, it is possible to develop significant vasospasm even during the first 3 days following SAH given that the 2 patients with the severe vasospasm must have gone through the "moderate" phase in the days preceding the angiogram on days 5 and 6. Admittedly the above assertions are based on small numbers and hence a study containing a larger number of patients with significant vasospasm would be more enlightening.

4. Correlation between other TCD parameters and angiographic vasospasm

TCD parameters such as maximum 1 day rise in velocity, number of consecutive days of velocity rise, the largest velocity difference in the same MCA segment on the same side or in any two segments on either side did not add to the information derived from the absolute velocities alone. This was true even when various parmeters were combined to increase the predictive value. The value of right – left velocity difference has been described in section I c above. However the means of all these parameters were higher in those with moderate / severe vs. none / mild vasospasm and the difference achieved statistical significance **(Table 7)** despite the lack of clinical usefulness. One reason for this lack of value is the large overlap in these parameters between the none / mild vasospasm group and the moderate / severe vasospasm group as is evident in the table. Hence these parameters discriminated poorly between the two groups despite and overall difference in the means.

II) THE INFLUENCE OF CLOT THICKNESS

Unlike the sensitivity and specificity, the PPV and NPV of a diagnostic test are influenced by the pretest probability of the disease which may simply be the prevalence of the disease. The probability of disease may be substantially modified by serial tests. In other words if a second test can modify the pretest probability by pre-selecting a subset of patients such that the likelihood of finding disease in them is higher or lower than in the original sample then the PPV or NPV of the test of interest would be improved. Hence the benefit of subsequent application of the test of interest may be enhanced. Therefore the influence of clot thickness, the strongest single predictor of subsequent vasospasm, was evaluated.

In 1980 Fisher et al. devised a grading system for the amount of blood seen on a CT scan acutely following SAH (155). They demonstrated a high degree of correlation between those with thick subarachnoid clots greater than 1 mm in thickness (Fisher grade 3) and the incidence of "severe" angiographic vasospasm and DIND. Similarly in the current study thick clots were associated with severe proximal or distal vasospasm with an odds ratio of 8.9 and with severe proximal vasospasm with an odds ratio of 9.1. However the association with moderate or severe vasospasm was weaker and in the absence of a larger number of patients than available in this study, only a trend toward statistical significance was demonstrated as described in "Results" (section III 1.). There was no association between clot thickness and DIND, perhaps because even moderate vasospasm can lead to DIND but the relationship between clot thickness and moderate vasospasm was weaker. This

discrepancy with Fisher's report may be due to the predominance of early aneurysm surgery and more common use of prophylactic HT in modern times.

There was no statistical difference between the tendency to develop moderate or severe proximally / distal vasospasm irrespective of whether or not the thick clot was present in Sylvian/interhemispheric fissure versus the basal cisterns only ($p = 0.77$). However when one considers only distal spasm, where clots localized to either the Sylvian or interhemispheric subarachnoid spaces would be in closer contact with M2 and A2 vessel segments, 36% vs. 14% developed distal spasm respectively. This trend did not reach statistical significance probably due to the small numbers involved.

As alluded to in section I e), the likelihood ratios for the effect of clot thickness on significant vasospasm could be used to enhance the PPV and NPV of the TCD velocities. However as seen in **Figures 13a and b**, the impact of such a strategy is minimal due to the relatively weak impact of clot thickness when moderate and severe angiographic vasospasm are considered together. Hence consideration of clot thickness is unlikely to have a significant impact on the post-test probability of moderate / severe vasospasm. Nevertheless the outlined arms in the flow diagrams highlight the ideal combination of TCD velocities and the clot thickness that would provide the clinician with optimal confidence for the presence or absence of significant vasospasm. Similar flow diagrams depict the role of clot thickness on the predictive value of TCDs in the diagnosis of *severe* vasospasm **(Figures 14a and b).** In this case its influence is greater due to a stronger (and statistically significant) association between thick clots and *severe* vasospasm as opposed to *moderate* /

severe vasospasm. The NPV of velocities < 200 cm/s wsas 96% versus 85% for the MCA and 77% for any of the MCA/ACA/SC-ICA, when the clot was thin. The PPV of velocities ≥ 200 cm/s was 80% versus 45% for the MCA, and 92% versus 57% for any of the three vessels, when the clot was thick. The above guidelines can prove useful for patients whose TCDs are < 120 or ≥ 200 cm/s. Only about half (43%) the patients met such criteria and only about a third (38%) fell in one of the outlined arms for predicting moderate / severe vasospasm. Hence clot thickness is a useful modifier of the post-test probability of *severe* vasospasm.

III) TCD – DIND CORRELATION

Eighteen percent of patients in this study experienced DIND, however as many as 20% may have developed it because 3 patients were considered to have possibly suffered DIND but the diagnosis was uncertain; however they did demonstrate significant angiographic vasospasm. The difference in the means of patients with and without DIND was statistically significant (section IV of *Results*). However maximum TCD velocities achieved prior to the diagnosis of DIND were not statistically correlated with DIND with cut-off points of 120 and 160 cm/s **(Table 8).** No patient with a velocity of < 120 cm/s developed DIND and hence the sensitivity and NPV of 100% at velocities of 120 cm/s or higher; however the specificity and PPV were both poor and therefore the clinical usefulness for diagnosing DIND was limited. Based on this data however one may be reassured that

the presence of DIND is highly unlikely if the maximum mean velocity reached has been < 120 cm/s. There was significant association at a threshold of 200 cm/s but the sensitivity and PPV were poor at 29% and 33% respectively. Therefore despite a NPV of 95% at this threshold, 71% of patients with DIND would not have been diagnosed as such by TCD criteria. The distribution of patients with DIND in the various TCD velocity categories was uniform: 4-5 patients in each of the 120-159, 160-199 and ≥ 200 groups. Thus TCD was poorly discriminative for diagnosing or anticipating the development of DIND in the vast majority of patients.

IV) ANGIOGRAPHIC VASOSPASM – DIND CORRELATION

The odds ratio for significant angiographic vasospasm as a risk factor for DIND was 8.7 and this was statistically significant. About a third or fewer patients with moderate or severe vasospasm in the anterior circulation developed DIND. Several putative explanations were proposed in section VI B of *Introduction* for this inconsistency. The prophylactic nature of HT in 40% of its recipients may have contributed to the relatively small fraction of patients with moderate or severe vasospasm who developed ischemic deficits.

Considering an average incidence of DIND to be 30%, the NPV of the absence of significant vasospasm on anterior circulation angiography for DIND, would be 91.4%. The remainder 8.6% would constitute those with posterior circulation vasospasm which was not studied as part of this investigation. In this

study, out of the 3 patients who developed DIND following the rupture of an aneurysm of the vertebrobasilar circulation, 2 demonstrated significant vasospasm only in the vertebrobasilar circulation without involvement of the anterior circulation. Hence it is important to angiogrpahically evaluate the posterior circulation in those with SAH due to vertebrobasilar aneurysm rupture if corroboration for the clinical diagnosis of symptomatic vasospasm is sought in these patients. Another point of note is that most of the patients (13/15) with DIND from anterior circulation spasm manifested significant spasm in the MCA, which is consistent with the previously noted finding that the MCA alone reflects any significant ongoing anterior circulation vasospasm fairly well. Seven percent of all the sides or 10% of the patients were found to have moderate or severe distal vessel spasm without such proximal involvement. None of these patients developed DIND. These figures are consistent with those reported previously (21, 58). Hence proximal vasospasm in the larger capacitance vessels seems to be more dangerous than that affecting the smaller distal vessels. This may be due to the ability of leptomeningeal collateral supply to compensate for the latter deficiency.

V) HYPERDYNAMIC THERAPY USE

About half the patients received HT and in 40% of the recipients it was prophylactic (i.e. these patients did not demonstrate any significant angiographic vasospasm). The highest absolute velocity reached was significantly higher during

HT than when no HT was administered among those who were administered HT, and it was also higher in those patients who received HT compared to those who did not. Given that HT use was not statistically correlated with the presence of significant vasopasm, the indirect implication is that HT may have an impact on absolute velocities by elevating them. Even after removing the possible confounding effects of co-existing vasospasm which was the reason behind the HT in a significant proportion of patients, by considering only those HT recipients who did not have concurrent significant MCA vasospasm, the effect persisted. This is conceivable based on the principles outlined previously in section IV. B) iii) of *Introduction*. The higher velocities may reflect higher cerebral blood flow due to HT. These results are consistent with a recent study by Manno et al. who demonstrated that induced hypertension could elevate TCD velocities (117). Causation however cannot be established and only an association can be speculated based on the current study due to its retrospective nature and the lack of effective control for other possible confounding variables; this would require a prospective cohort or a randomized controlled study.

In part II of the study, Lindegaard ratio during HT versus during no HT, among HT recipients, was also not significantly different. This implies that the poor correlation between TCD (both absolute velocities and Lindegaard ratios) and angiographic vasospasm may not be solely due to the potential confounding effect of HT and is probably also related to the numerous other variables that may also influence TCD as outlined in section IV B of the *Introduction*.

VI) OTHER VARIABLES THAT MAY INFLUENCE VELOCITIES

Section VII) of the *Results* compares extraneous factors other than vasospasm that may potentially impact on TCD velocities and hence by chance may have caused velocities to be higher in the none / mild vasospasm group thereby diminishing the positive predictive value and specificity of high velocities as seen in this study. Only blood pressure has been shown to directly influence the velocities (117) and the vast majority of patients (91/101) had values available for this parameter. None of the extraneous variables, including the MAP, were significantly different between those with moderate / severe and those with none / mild vasospasm. This finding reassures against the potential confounding effects of these variables and suggests that the relationship between TCD velocities and angiographic vasospasm discovered in this study represents the true interaction between just these two tests.

VII) RISK FACTORS FOR VASOSPASM

Initial clot thickness is considered to be the strongest predictor of subsequent angiographic vasospasm. The impact of clot thickness was discussed in section II.

Clinical status has also been associated with angiographic vasospasm (156). In this study clinical grade on admission did not correlate with either moderate / severe or severe angiographic vasospasm. This may be because the initial pre-resuscitation grades were used. These may have been misleadingly high because of the adverse

impact of hydrocephalus on the patient's admission status in a significant proportion as the majority of patients had some degree of hydrocephalus on admission.

VIII) INCLUDED VERSUS EXCLUDED PATIENTS

In Part I of the study 25 patients were excluded because follow-up angiography was not performed. As indicated, these patients were either doing "well" or "poorly" and did not warrant an angiogram. Patients in whom the chance of significant vasospasm is remote are appropriately excluded since the clinical course of these patients is not typically complicated and therefore TCD is generally not useful in this setting as it does not alter the management of these patients. Similarly TCD exams would not be beneficial in patients who are moribund and therefore who are not candidates for further investigations or treatment. By studying a sample of patients that is similar to the population in which the test will actually be used, sampling bias was minimized in this study. This issue was also addressed by calculating likelihood ratios which allows for the calculation of post-test probabilities based on various pre-test probabilities or prevalence of vasospasm. In part II, 6 of the 8 patients were excluded due to the absence of TCD exams. This is a reflection of a transient scarcity of TCD personnel during this time period.

Demographic factors, clinical grade and the proportion of patients with thick clots were not significantly different between the included and excluded patients **(Table 10).** The proportion of patients receiving HT and albumin specifically was

lower in the excluded group but this did not achieve statistical significance. However in keeping with the superior clinical status of the majority of patients in the excluded group, none of them developed DIND and therefore none received inotropes or vasopressors. The mean highest velocity reached was significantly lower compared to that for the included patients. They also received albumin for fewer days than the patients in the included group. Fewer TCD exams were performed in the excluded group; this too is consistent with the generally healthier status of the excluded patient.

PART II

Although the overall mean Lindegaard ratio was higher in patients with moderate or severe vasospasm and there was a statistically significant association, the PPV was only 63% and the NPV was 89%, neither one of which is better than the corresponding value for the absolute velocities. The sensitivity of a Lindegaard ratio > 3 to diagnose significant vasospasm was only 45%; at a lower threshold, the specificity and hence the PPV would decline even further. Lindegaard ratios were found not to be helpful in establishing DIND. Hence Lindegaard ratio did not add any information to that obtained from absolute velocities alone. This may be because the numerous factors (outlined in section IV B of "Introduction") other than blood flow

that can confound the interpretation of absolute velocities, also apply to the interpretation of Lindegaard ratios. In addition, the assumption that the SC-ICA and the MCA are part of a single flow circuit in continuity is not entirely accurate because the A1 segment of the ACA may carry a significant portion of the flow. Therefore in the presence of MCA spasm, flow more proximally may not be substantially diminished if it is preferentially diverted to the A1 segment. Spasm may affect the SC-ICA and therefore the MCA velocity rise due to MCA spasm may be attenuated due to increased resistance more proximally. Similarly the velocity in the extracranial ICA may be higher due to local stenosis secondary to atherosclerosis. This may impede blood flow distally in the MCA thereby lowering the velocity despite vasospasm. The Lindegaard ratio would be smaller and falsely negative in this situation.

CHAPTER 5: CONCLUSIONS

The precise contribution of transcranial Doppler ultrasonography to the diagnosis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage has been debated. Neurosurgical centers around the world rely on this modality to make critical management decisions in the above setting every day. Velocities greater than 120 cm/s are commonly considered to be "high" and therefore indicative of vasospasm requiring further investigations or treatment. However the data from this study demonstrates that only the very low (<120 cm/s) and the very high (≥ 200 cm/s) absolute velocities can be depended upon in the diagnosis of clinically important vasospasm. Velocities for the majority of patients fall in the intermediate range of 120 – 199 cm/s which, although considered to be abnormally "high", are misleading and cannot be relied upon to consistently indicate the presence of vasospasm that requires treatment or further investigation. TCD should therefore not be used to define "vasospasm" in clinical studies. Clot thickness on the initial CT scan of the brain obtained within 2 days of the SAH can be useful to augment confidence in the presence or absence of vasospasm based on TCD velocities.

If likelihood ratios for other potentially helpful tests (e.g. CBF studies, CT angiography) could be studied then it may be possible to reliably and consistently detect impending vasospasm without the need for digital subtraction angiography (DSA) in a greater proportion of patients. The ideal test or combination of tests will be able to distinguish hemodynamically significant from inconsequential vasospasm

prior to the onset of ischemic deficits and at the same time pose little risk to the patient. Besides being invasive, DSA cannot be used to continually monitor the patient for vasospasm as it is limited to providing a single snapshot in time that by chance may or may not capture existing vessel narrowing. It also does not directly reflect the hemodynamic impact of the spasm.

Neither absolute velocities nor Lindegaard ratios correlate directly with the diagnosis of DIND. Lindegaard ratios do not add to the information provided by absolute velocities alone for the diagnosis of angiographic or clinical vasospasm. Absolute velocities may be helpful for establishing the presence of DIND if the diagnosis is suspected clinically and the velocities are ≥ 200 cm/s. Hyperdynamic therapy may serve as a confounding variable by artificially elevating TCD velocities although further study is necessary. The relationship between Doppler velocities and blood flow is probably far more complex and it would be simplistic to attempt an explanation based solely on the radius of the vessel and the patient's fluid status or the administration of inotropes / vasopressors. This relationship will undoubtedly continue to unravel as more studies on the subject of TCD and cerebrovascular physiology are pursued.

Despite clarification of the reliability of TCD in the diagnosis of significant angiographic vasospasm, its precise role in the setting of SAH remains obscure given that the benefit of prophylactic hyperdynamic therapy in patients with radiologic vasospasm (diagnosed either by TCD or angiogram) who are *asymptomatic* has not been established in a randomized trial. The few studies performed using weaker designs and from which conclusions cannot be derived due to the lack of a control

group, have produced conflicting results (79, 122, 123, 157). The natural history of such asymptomatic patients with vasospasm is also not clearly known. Hence it is possible that instituting treatment promptly at the first sign of DIND in patients who can be followed clinically, may not be any worse than early prophylactic treatment for *asymptomatic* patients with radiologic evidence of vasospasm. If TCD is used to confirm clinical suspicion of vasospasm in symptomatic patients then its benefit is limited to those with DIND ***and*** velocities ≥ 200 cm/s, which form a small proportion of patients. Moreover these patients may require angiograms anyway to clarify the nature and distribution of vasospasm or to perform angioplasty or administer intra-arterial papaverine. Therefore it can be argued that the only truly useful application of TCD may be in patients whose neurologic status is so poor that serial clinical exams cannot be relied upon to detect ongoing cerebral ischemia due to vasospasm. TCD may alert the clinician to the presence of "symptomatic" vasospasm in these patients that may not overtly manifest itself due to a poor pre-existing baseline condition.

Ultimately the true value of TCD in the setting of aneurysmal SAH can only be determined by a randomized controlled trial of this test by randomly assigning one group of patients to receive this test and another to not get this test. Only then may one be able to answer questions such as: Is there a decreased incidence or duration of ischemic deficits due to earlier vasospasm diagnosis and hence treatment? is there a reduced need for confirmatory angiograms? Is the hospital stay shorter? And most importantly, do they have a better outcome?

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